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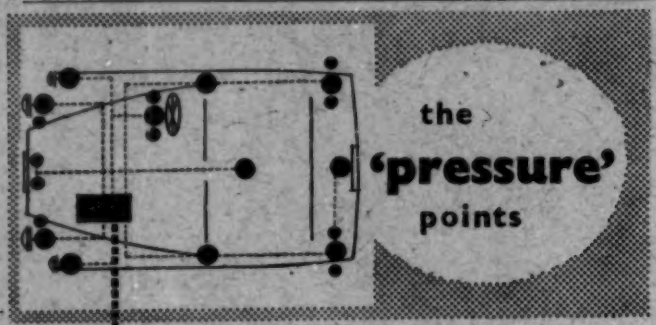

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 26 1955

# HYPERPARATHYROIDISM WITH RENAL CALCINOSIS

BY

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Clinical knowledge of hyperparathyroidism can be said to date from the successful removal of a parathyroid adenoma in a case of hyperparathyroidism by Mandl in 1926. Since that time Albright and his associates (1929, 1934, 1936, 1937, 1938, 1941, 1948) have played a leading part in advancing our knowledge of the disorder, particularly in regard to the chemistry and to the involvement of the kidneys. It is from the latter angle that we wish to present an interesting case. The problem is not free from complexity, in so far as primary hyperparathyroidism (whether due to a parathyroid adenoma or general parathyroid hyperplasia) may cause renal calcinosis with ultimate renal insufficiency; and, on the other hand, renal insufficiency from any cause, associated with retention of phosphorus and with high plasma inorganic phosphorus, may be followed by hyperplasia of the parathyroid glands, which from a teleological point of view has the purpose of an attempted elimination of the (excessively) retained phosphorus, the primary action of parathyroid hormone being believed to be augmented elimination of phosphorus.

Further, whatever the nature of the primary renal lesion may be, the secondary hyperplasia of parathyroid glands may lead to renal calcinosis and sometimes to osteoporosis. Unless, therefore, the whole history of any one case is known and the case has been investigated in its early as well as its late stage, it may be difficult, or impossible, to state in the terminal phase whether the condition was primary hyperparathyroidism with secondary renal involvement or primary renal disease with secondary parathyroid involvement. Renal calcinosis as a consequence of primary hyperparathyroidism is not only met with clinically but has also been produced experimentally (Hueper, 1927; Leberman, 1940). The calcium may be deposited profusely in minute particles both in the renal parenchyma and in the tubules, and/or renal calculi of variable size may be visible radiologically.

In some urological clinics it is an obligatory routine to test for hyperparathyroidism in every case of renal calculus, and experience has shown that such calculi need not be obviously multiple or bilateral. Perhaps the most complex case of all is the one starting with a parathyroid adenoma with secondary renal calcinosis, in which the adenoma is successfully removed, but, nevertheless, the renal calcium deposits do not disappear and the damage already done to the kidney is irreversible and even progressive, so that the condition progresses to renal insufficiency, and, secondary to this, there is hyperplasia of the remaining parathyroid glands, the patient ultimately dying in uraemia. Such appears to be the sequence of events in the case here presented.

## Case History

A woman of 40 was admitted to a surgical ward of Willesden General Hospital in September, 1941, under Mr. F. W. M. Pratt, with a firm swelling in the middle of the right tibia, said to have followed slight trauma in that area six months previously.

*X*-ray examination was carried out on September 4 and the radiological report (Dr. Rohan Williams) was as follows: "On the anterior aspect of the shaft of the right tibia, extending over a length of 3 cm., there is a destructive bone lesion associated with minimal swelling of the soft tissues. The bone destruction is confined to the cortex and there is no reactionary new bone formation. The appearances are suggestive of a malignant bone tumour or possibly the rather rare subperiosteal type of osteoclastoma" (Fig. 1).

Mr. Pratt explored the swelling, found a soft-tissue mass under the periosteum, and took out a piece for biopsy. Pathological report: "Typical osteoclastoma." Mr. Pratt then undertook a wedge resection of the tumour. Pathological report: "Wedge of bone with elliptical piece of skin and subcutaneous tissue over one part. To one side beneath the soft tissues is a small deep red 'tumour' extending about 1.5 by 0.5 cm. Microscopy: The histology of the tumour is similar to that of the biopsy—an osteoclastoma. There is some coarse-fibred bone at the periphery of the tissue."

The wound healed and the patient was seen again by Mr. Pratt in September, 1942, with a history of swelling of the left forearm, following trauma. The radiological findings (Dr. Rohan Williams) were as follows: "(1) Left ulna: Two distinct osteolytic cyst-like areas are present in the shaft of the ulna. At each site the cortex is appreciably thinned by the cystic process and there is diffuse decalcification of the forearm bones (Fig. 2). (2) The skull shows a widespread stippled type of osteoporosis affecting the whole calvarium, being especially marked in the fronto-parietal regions (Fig. 3). It should be noted that this lateral radiograph of the skull was taken with 60% of the normal exposure, and, even so, the region of the vault on the film

has been subjected to chemical reduction. (3) Other bones: There are several areas of localized bone destruction—for example, in the left ilium near the sacro-iliac joint, the left lesser trochanter, and the left pubic bone. (4) There is considerable generalized osteoporosis of the skeleton with marked cortical thinning."

The findings appeared to be typical of generalized osteitis fibrosa cystica (hyperparathyroidism), and Mr. Pratt asked one of us (S. L. S.) to investigate and advise from this standpoint. The more recent past history, apart from the bone incidents, included constipation, weakness, dyspnoea, and insomnia. The patient was thin and had a small swelling in the lower region of the left lobe of the thyroid gland. There were no signs of thyrotoxicosis. B.P. 120/80. Fundi normal. Urine normal. Serum calcium, 15.8 mg. per 100 ml.; plasma inorganic phosphorus, 2.5 mg. per 100 ml.; plasma alkaline phosphatase, 65 K–A units per 100 ml. Urinary calcium over a three-day period on a daily intake of 100 mg. of calcium was 1,232 mg. Radiographs of the renal tract showed a single small calculus in the lower pole of the left kidney and several small stones in the right kidney (upper half).

FIG. 1.—Radiograph taken on September 4, 1941, showing the bone lesion in the right tibia.

The diagnosis of hyperparathyroidism explained all the features, and it was decided to explore the under surface of the left lobe of the thyroid gland for a parathyroid tumour, although the latter rarely presents as a palpable swelling. However, a yellow lobulated parathyroid tumour was found by Mr. Pratt at that site, and removed (October, 1942). Pathological report: "Nodular tumour 2.5 by 1.2 by 1.8 cm. Weight after fixation, 4.4 g. Cut surface: fibrous capsule and deep buff-coloured rather friable soft contents. Some of the material had fallen out, leaving a slightly cystic appearance. Microscopy: a rather uniform tissue resembling normal parathyroid, composed of close-set cells, mainly transitional and water-clear in type. The cells are arranged in masses of varying size, with fine connective tissue septa" (R. R. W.).

FIG. 2.—Radiographs taken on September 14, 1942, showing diffuse decalcification of the forearm bones.

Immediate post-operative biochemistry: serum calcium 8.9 mg., plasma inorganic phosphorus 5 mg., alkaline phosphatase 65 units per 100 ml. Six months later: serum calcium 10 mg., plasma inorganic phosphorus 2 mg., alkaline phosphatase 6.7 K–A units per 100 ml. For some weeks after operation the patient had mild tetany, relieved by calcium and calciferol. Less definite paraesthesias persisted in the next few years, and calciferol, 300 units daily, was given intermittently. One year after operation the radiological bone changes tended to revert to normal: "There is an almost spectacular regeneration of bones within the open areas. Appearance of the upper ulna suggests healing of pathological cystic fracture." Serum calcium 9.9 mg., plasma inorganic phosphorus 2 mg., and alkaline phosphatase 6.7 K–A units per 100 ml.

The patient attended at infrequent intervals at the out-patient department, but the notes do not indicate any serious complaints or findings in 1943 or 1944, and the blood pressure was normal 120/80. In January, 1945, the serum calcium was 11.8 mg. and plasma inorganic phosphorus 3.7 mg. per 100 ml. In October the patient complained of headaches. The blood pressure was 150/90. The serum calcium was 9.8 mg., plasma inorganic phosphorus 6.6 mg.,

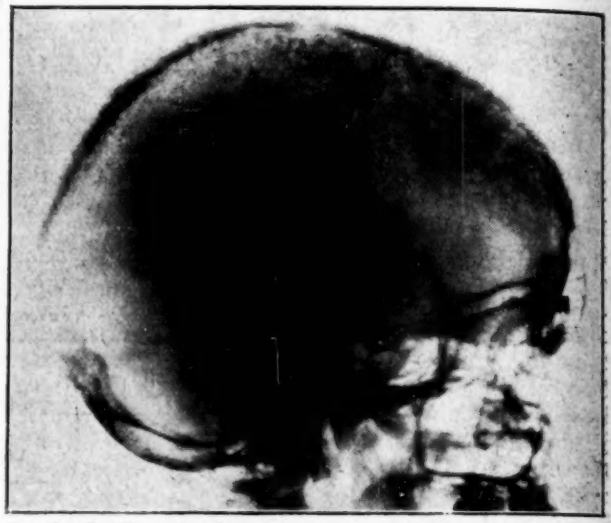

FIG. 3.—Radiograph taken on September 14, 1942. A widespread stippled type of osteoporosis is shown, affecting the whole calvarium, especially the fronto-parietal regions.

and alkaline phosphatase 7 K–A units per 100 ml. The raised plasma phosphorus indicated renal impairment. At this time radiological examination showed partial bony obliteration of the cystic changes in the left ulna. In general, the long bones showed normal architecture, but there was mottled osteoporosis of the skull, vertebrae, iliac bones, and the ribs. The osteoporosis was somewhat unexpected in view of the normal alkaline phosphatase.

The patient was not seen again until June, 1946, when she was admitted to hospital after falling off a bus and bruising her right arm. Apart from this, her complaints were dimness of vision and swelling of the ankles in the past few weeks. At this time, however, the florid picture of azotaemic nephritis with cardiovascular hypertrophy was obvious: B.P. 240/160; bilateral papilloedema with albuminuric retinitis and exudates in the fundi; albuminuria with granular, hyaline, and epithelial casts; blood urea 86 mg., 94 mg.; urea clearance only 18% of normal; and severe secondary anaemia. The serum calcium was 12.8 mg. and plasma inorganic phosphorus 8 mg. per 100 ml., the latter high value being due to poor renal function. Radiological examination again showed marked generalized decalcification of all the bones. The plasma phosphatase was reported as only 5 K–A units and again 7 K–A units. Calcium urinary excretion over a 72-hour period, with a daily intake of 100 mg., was 854 mg. Radiography showed metastatic calcification scattered in both kidneys. It was concluded that the original renal calcinosis had led to destruction of renal parenchyma and to renal insufficiency, which, in its turn, had led to secondary hyperplasia of the remaining parathyroid glands.

As there were no obvious remedial measures available the patient was allowed to go home, as she requested, and was admitted a few months later (October, 1946) with incessant vomiting, soon terminating in uraemic coma; blood urea, 224 mg. per 100 ml. (A specimen of blood taken ten minutes after death showed serum calcium 18.4 mg. and urea 520 mg. per 100 ml.)

### Necropsy Findings

A rather thin woman with pale skin and grey-brown hair. Cyanosis of lips. Post-mortem staining of lower abdominal wall.

*Cardiovascular.*—The heart (397 g.) showed some hypertrophy of the left ventricle. The aorta and the coronary and cerebral arteries were only slightly atheromatous.

*Respiratory.*—Moderate congestion and oedema of lungs.

*Alimentary.*—The liver was small (1,060 g.) but appeared normal. The pancreas showed post-mortem autolysis. This system was otherwise normal.

*Haemopoietic and Endocrine.*—The spleen was small (85 g.) but of normal appearance. Lymph nodes—no abnormality noted. The *thymus* measured 10.5 by 2.3 by 0.5 cm. (No sections of thymus were taken.) The *thyroid* was normal in size and appearance, as were the *adrenals*. Two *parathyroids* were found, both on the right at the lower pole of the thyroid. The anterior and larger measured 3.5 by 1.2 by 1.5 cm.; it was coarsely lobulated, partly pale and partly dark red. The cut surface was a pale creamy colour mottled with dark red. The smaller posterior parathyroid measured 2 by 1 by 0.8 cm. and resembled the other. The *pituitary* was enlarged by a roundish lobulated pale tumour 2.2 by 2 by 2.5 cm., the larger part of which was above and outside the sella turcica. The optic chiasma was stretched over the posterior part of the tumour, which had a pale homogeneous cut surface.

*Urinary.*—The kidneys were markedly contracted, the right weighing 70 g. and the left 60 g. The subcapsular surfaces were granular, the granules being pale. On section the cortex was grossly reduced, the maximum thickness being 5 mm.; the pattern was indistinct, with a stippling of deposits of calcium; tiny calculi were found in some small cortical cysts. The medulla was also stippled with calcium deposits. The cortico-medullary boundary was blurred. The bladder contained alkaline urine with a deposit of triple phosphates and amorphous urates.

*Genital.*—The uterus, ovaries, tubes, and external genitalia were normal. The mammary glands exuded a milky fluid when cut; this fluid contained 24 mg. of calcium per 100 ml.

*Nervous.*—There was a cerebellar pressure cone, and the anterior perforated substance was indented by the pituitary tumour.

*Osseous.*—The calvarium was up to 1 cm. thick; there was some loss of demarcation of outer and inner tables, with obliteration of diploë. The *right humerus* was externally normal, but on the cut surface of the lower part of the head and surgical neck there was an irregular area of 2.5 cm. in diameter, which was solid, and white in colour with red patches. The upper end of the shaft of the *left ulna* was expanded to a diameter of almost 3 cm. over a length of 3.5 cm.; the upper third of the shaft was slightly bowed and slightly angulated on the distal two-thirds. The expanded part had a cut surface of deep red with greyish markings; the cortex in this region was reduced to 2 mm. thick in places. The upper part of the shaft of the *right tibia* showed slight thickening of the cortex and an increase in medullary trabeculation.

These bones were radiographed after removal. The ulna showed "major cystic changes with expansion in upper third of diaphysis with medial bowing, maximal at level of cyst." In the tibia "the merest traces remain of an old destructive process: some medullary calcification of a non-osseous type is present." In the humerus there were "irregular intramedullary calcific deposits in the surgical neck with some ill-defined cancellous bone destruction—no demarcated cyst wall" (Dr. E. Rohan Williams).

### Microscopy

*Parathyroids* (Fig. 4).—The enlarged glands are composed almost entirely of transitional and water-clear cells, arranged in solid masses closely set together, so that the tissue is decidedly compact. There are very few oxyphil cells.

*Bones* (Fig. 5).—The cortical bone is much more open in structure than normally, owing to marked osteoclasis. Haversian canals in the ordinary sense are not seen. In their place are much larger and more irregular spaces, filled by fibrous tissue of varying cellularity. The bony tissue itself is correspondingly irregular in disposition and reduced in amount, besides showing changes indicative of rapid resorption and reformation. There are many cement lines, often irregularly arranged and often ending at surfaces; the bone is mostly woven or coarse-fibred. Osteoclasts are numerous, osteoblasts less conspicuous. The bone marrow is widely replaced by an abnormal bony tissue with intermingled fibrous tissue. The reddish mass expanding the upper end of the left ulna is composed mostly of fibrous tissue, of widely varying cellularity, with scanty spicules of bone embedded in it, some of which are being formed, some being eroded.

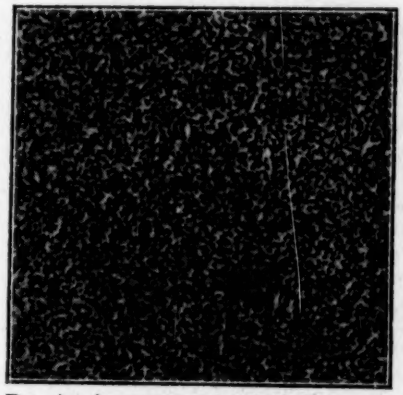

FIG. 4.—A representative field from one of the enlarged parathyroids found at necropsy. (H. and E. ×105.)

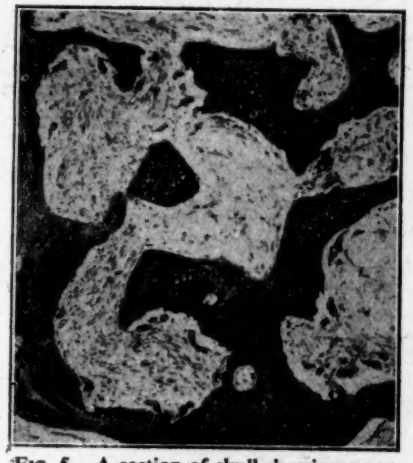

FIG. 5.—A section of skull showing many osteoclasts eroding woven and lameliar bone, with fibrosis of marrow. (H. and E. ×56.)

*Kidneys* (Fig. 6).—Fifty per cent. of all *glomeruli* are converted into scarred structures, more or less completely hyaline; they lie in hyaline rings, originally Bowman's capsules, and are typical of the ischaemic or arteriosclerotic kidney. Some of them show slight or moderate granular calcification. Nearly 40% of all glomeruli show partial hyalinization of their tufts; but none

FIG. 6.—Kidney. Calcification of arterial walls and of tubular basement membrane. (H. and E. ×190.)

of these aforementioned glomeruli, comprising 90% of the total, show any of the changes associated with glomerulotubular nephritis. The remaining glomeruli show, often in addition to the lesions of the second group described above, focal necroses, adhesions, and capsular endothelial swelling. Some of these glomeruli have afferent arterioles showing fibrinoid necrosis. These lesions are of the kind seen in malignant hypertension. The *tubules* show alternating islands of atrophy and hypertrophy. In the atrophic parts the remaining tubules are embedded in fibrous tissue which is generally poor in cells. The tubular basement membrane is sometimes calcified. Many *arteries* of varying size show slight, moderate, or marked calcification of intima and/or media. The arcuate and interlobular arteries show intimal and medial thickening of varying degree; in some cases the lumen is totally obliterated. A few of the smaller arteries show fibrinoid necrosis. Calcification of connective tissue in the cortex affects mainly the fine fibres surrounding tubules, both normal and atrophic; in the medulla it occurs in scattered foci. There is patchy lymphocytic infiltration in both cortex and medulla.

*Pituitary.*—The enlargement is due to a chromophobe adenoma. The remains of the gland are compressed into a crescent about 2.5 mm. thick, in which the normal pituitary cell types are readily recognized.

*Other Organs.*—Metastatic calcification is found in the vessels of the ovary, uterus, spleen, and myocardium, and in the connective tissue and muscle fibres of the heart. In the vessels of the organs mentioned calcification affects the media, the internal elastic lamina, and the intima, but not necessarily all of these in any one instance. No relationship can be discerned between the distribution of calcification in the vessels of the heart and its distribution in the muscle fibres. Calcification affects the whole cross-section of the muscle fibres, but not the whole length.

The lungs show confluent bronchopneumonia.

### Comment on Pathological Findings

Three matters require discussion: (1) the nature of the enlargements of the parathyroids; (2) the renal changes; and (3) the concomitant enlargement of more than one endocrine organ.

(1) The original parathyroid mass that was surgically removed is regarded as an adenoma because it was encapsulated, because no other enlarged parathyroid was found at that time, and because its histology was clearly that of neoplasia and not primary hyperplasia (Castleman and Mallory, 1935). Correspondingly the enlarged parathyroids found at necropsy are regarded as showing secondary hyperplasia, because they were multiple and their histology fits the descriptions given by Castleman and Mallory (1937), Gilmour (1947), and Fritz and Brines (1951), in studies of parathyroid changes following renal disease.

(2) The renal changes in this case are very similar to those described by Anderson (1939) in his study of the renal lesion in hyperparathyroidism, and to those of Case 3 of Morgan and Maclagan (1954) in which bony and renal changes were caused by a parathyroid adenoma. Both papers drew attention to the absence of changes indicative of Bright's disease. In Anderson's paper there is a photograph of calcified tubular basement membrane closely resembling our Fig. 6. As to the terminal uraemia in our case, there can be no doubt that the degree of renal damage was adequate to account for almost complete loss of renal function.

(3) This case presented a parathyroid adenoma, a pituitary adenoma, and an enlarged thymus. Such a state of affairs is rare, but a few other such cases have been reported, and it may be that this kind of condition will be more frequently observed in future now that it has been noted, as has happened in other matters.

Underdahl, Woolner, and Black (1953) described 14 cases from the literature in which a pituitary tumour was associated with hyperplasia and/or neoplasia of the parathyroids, clinical hyperparathyroidism being present in four of the cases and the remainder apparently lacking clinical data. The majority of the patients were acromegalics, but two, without acromegaly, had pituitary chromophobe adenomas. Parathyroid adenomas were both single and multiple. In four acromegalics there were also present multiple adenomatous islets of Langerhans, in association with general hyperplasia and hypertrophy of the islets. Hypoglycaemia was a feature in two such cases. Underdahl and his colleagues further described eight cases from the Mayo Clinic in which "multiple adenomas and adenomatosis of the parathyroids and pancreatic islets" were the usual findings, together with chemical and often clinical hyperparathyroidism and hypoglycaemia. In four of these cases there was no evidence of a pituitary tumour; in two the diagnosis was acromegaly, and in two chromophobe adenoma; one of the latter showed no pituitary clinical manifestations, and the other, a male, showed hypogonadism. The coexistence of neoplasia with hyperplasia in the pancreas and parathyroids is possibly in keeping with the theory (Simpson, 1951) that neoplasia of endocrine glands may follow hyperplasia. The chromophobe character of the pituitary cells, in some cases, may be secondary to an initial chromophil state. The question whether the pituitary lesion was primary or merely associated remains unanswered.

Black and Ackerman (1950), reviewing 23 cases of parathyroid tumour, reported one case which had also pancreatic and adrenal tumours, and another with tumours also of the pituitary, thyroid, adrenals, and pancreas.

In our case there was apparently enough residual pituitary for normal function, because the adrenal cortex was not atrophic, nor was the thyroid, and there were maturing follicles in the ovaries.

We have found the thymus involved in only one report, that of Bergstrand (1922). In each of his two cases the thymus was regarded as hyperplastic, and in each case both the inferior parathyroids contained small adenomata. No skeletal abnormalities were noted. Unfortunately no sections were prepared from the thymus in our case. Regarding the apparently functionless state of the parathyroid adenomata in Bergstrand's cases, it is worth noting that Hadfield and Rogers (1932) also reported two cases of parathyroid tumour without osteitis fibrosa, one being an acromegalic; and four of the surgical cases of Underdahl *et al.* (1953) mentioned above had no discernible skeletal involvement, though they showed positive chemical findings.

## Discussion

As has been indicated above, Albright and co-workers were the first to indicate the importance of renal involvement in hyperparathyroidism, a finding which might well have been anticipated from the experimental work of Hueper (1927), who demonstrated metastatic calcification in organs such as the kidneys, lungs, and stomach, in dogs dying of acute parathyroid poisoning. Cope (1942) reported renal calculi in no fewer than 47 of 67 proved cases of hyperparathyroidism.

Johnson (1939) described a case with the title "primary hyperparathyroidism with extensive renal calcification and secondary hyperplasia of the parathyroids." The patient was a man of 34 who had suffered for two years from weakness, loss of weight, thirst, and polyuria. He entered hospital following a fracture of a cystic right humerus after very slight trauma. Serum calcium was 15.7 mg., plasma inorganic phosphorus 2.6 mg., and plasma phosphatase 34 Bodansky units per 100 ml. Blood urea was normal, but some areas of calcification were noted in what was described as a horseshoe kidney. A parathyroid adenoma was removed, and after a period of mild tetany the blood chemistry returned to normal and the patient was not seen for a period of four years. He then returned with hypertension and uraemia and renal insufficiency, dying in uraemic coma. The renal insufficiency distorted the blood chemistry, so that the serum calcium was only 10.5 mg. and the plasma inorganic phosphorus was above normal—namely, 6 mg. Necropsy showed gross hyperplasia of the remaining three parathyroid glands which could only be regarded as

secondary to the renal insufficiency, nephrocalcinosis, with hyalinization of the glomeruli and deposition of calcium in the tubules and interstitial cells.

Downs and Scott (1941) reported a similar case with the title "hyperparathyroidism with adenoma causing renal failure and secondary hyperparathyroidism." This patient, however, presented in the late stages as a case of renal colic and severe renal insufficiency with terminal uraemia; and the necropsy finding of one parathyroid adenoma and hyperplasia of the remaining parathyroid glands led to the diagnosis and reconstruction of the disease as indicated by the title. The renal insufficiency, in this case also, distorted the calcium and phosphorus values, which were respectively 5.8 mg. and 7.6 mg.—another difficulty in making the diagnosis when renal insufficiency had led to severe phosphorus retention and secondary depression of an initially raised serum calcium.

In our case, although renal calcinosis was present initially, there was every indication that renal function was at that time normal. The blood pressure and the blood urea were normal and there was no cardiovascular hypertrophy. Further, the removal of the parathyroid adenoma led to post-operative parathyroid insufficiency and mild tetany, which would have been unlikely if the remaining parathyroid glands were hyperplastic at the time of the operation. However, although we lost touch with the patient there was no evidence that the calcium deposits in both kidneys ever disappeared, and the changes that they had already produced in the renal parenchyma were probably of sufficient severity to lead to a progressive involvement of the kidneys and finally to renal insufficiency. At a certain point along this road, the remaining parathyroid glands underwent hyperplasia in an attempt to eliminate the retained phosphorus. The high serum calcium value and the low plasma inorganic phosphorus value at the time when the patient was first seen also indicated that the kidneys were then not seriously impaired. In the terminal phase, although parathyroid hyperplasia and hyperfunction were undoubtedly present, the serum calcium was normal, the depression of the raised serum calcium being secondary to the high plasma inorganic phosphorus.

Hellström (1950), in a review of this subject, states: "The prognosis following parathyroidectomy in hyperparathyroidism is chiefly dependent upon the degree of renal damage at the time of operation; the skeletal changes are of less importance. A certain improvement of the renal damage is possible after parathyroidectomy, but in most cases the damage is lasting or shows progression." He further states that "evaluation of the prognosis calls for a long follow-up period, since the patients may be apparently healthy for many years but ultimately die from sequelae of hyperparathyroidism, even if the latter has been checked by parathyroidectomy. The renal damage is an early symptom of hyperparathyroidism and is mainly due to calcium deposition in the tubular epithelium and to vascular changes leading to nephrosclerosis."

From our own case and from the study of the literature we would associate ourselves with the opinion here stated, which was based on a series of 21 cases.

### Summary

A case of hyperparathyroidism is described in a woman of 40, presenting itself initially as an osteoclastoma of the tibia. There was also radiological evidence of renal calcinosis secondary to the primary hyperparathyroidism. Removal of a causative single parathyroid adenoma was followed by transient tetany and subsequent return of the blood chemistry to normal. Four years later, however, the patient returned with severe renal insufficiency and terminal uraemia. Necropsy showed nephro-sclerosis with multiple calcium deposits; and hyperplasia of the remaining parathyroid glands, secondary to the renal insufficiency. Primary and secondary hyperparathyroidism therefore occurred in the one patient at different phases of the disease. In view of the bad ultimate prognosis of primary hyperparathyroidism with secondary renal involvement, through multiple calcium deposits, the importance of diagnosing primary hyperparathyroidism early, and before such renal involvement, is indicated.

The associated finding of a pituitary chromophobe adenoma is also recorded and discussed.

It is with great pleasure that we express our acknowledgments and thanks to Mr. F. W. M. Pratt, who carried out all the surgery, and under whose initial care the patient came; to Dr. E. Rohan Williams for the radiological reports and illustrations, to Dr. G. E. Harre, who carried out the necropsy and initial biopsy studies, and to Dr. G. M. Smith for chemical pathology.

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# DIABETIC AMYOTROPHY*

BY

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Although neurological complications of diabetes have been recognized for almost a hundred years, they have not received the detailed attention usually given to neurological disorders, nor the attention they deserve. That they are common is beyond doubt. Joslin *et al.* (1952) saw 913 diabetics with neurological syndromes in one hospital during a five-year period; this list included a number of disorders of the nervous system which were probably coincidental, but 519 consisted of syndromes of areflexia, paraesthesiae, pain, weakness, and wasting, most of which were almost certainly by-products of diabetes. More recently Matthews (1955) has found evidence of "neuropathy" in 37% of 545 unselected diabetics. Since the total number of diabetics in the world is said to be about twenty million it would seem that "diabetic neuropathy" may include millions of victims. The term "neuropathy" is used rather loosely, sometimes referring to disturbances of peripheral nerves only (in the previous sense of "neuritis") and sometimes more widely to include motor and sensory disorders resulting from lesions of the spinal cord,

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peripheral nerves, or both; it ought to be restricted to disorders of peripheral nerves only, "myelopathy" being used when the cord alone is involved, and "myeloneuropathy" when both cord and nerves are affected; though this distinction is arbitrary on clinical grounds without histological proof.

For over half a century it has generally been accepted that diabetic neuropathy is characterized by ill-localized pain, paraesthesiae, areflexia, and sensory loss tending to be peripheral, bilateral, and symmetrical—in other words, the picture of diabetic "polyneuritis" or "pseudo-tabes." The literature only occasionally records signs or symptoms which appear to be of root or cord origin, and only rarely have histological changes in the cord been described. In March, 1950, I observed a patient who was suffering from a purely motor disorder which was clearly of cord origin and associated with diabetes; although unfamiliar with this combination, I felt that it was probably a syndrome. In the following June I saw an almost identical picture, and was satisfied that these were two examples of diabetic myelopathy; after three more patients had been observed the condition was recorded (Garland and Taverner, 1953).

At that stage it seemed that the syndrome consisted of the following. The patients were all over 50 years old, the history of diabetes was short and the degree not severe. The neurological picture was limited to the legs, and included diffuse pain, weakness, wasting, and loss of tendon-jerks, which were usually asymmetrical. Less constant features were extensor plantar responses, a raised protein content of the cerebrospinal fluid (C.S.F.), and electromyographic changes in the affected muscles compatible with a cord lesion and unlike the usual changes of a peripheral neuropathy. In none was there any sensory loss. It was felt that the myelopathy probably resulted from disordered metabolism, and it had arisen only in patients who, though usually being treated, had not been under full diabetic control. It was also clear that the disability could continue to deteriorate after full diabetic control had been achieved, but at the same time the syndrome was largely or totally reversible. In four of the five original cases a neurological diagnosis had already been made by a physician, always incorrectly. A search through the literature soon revealed that this was no new discovery but that the condition had been described in three patients by Bruns (1890) in Germany; moreover, he had been able to achieve reversal of the disorder by dietetic restriction only.

## Follow-up of Original Cases

Since 1953 further observations have been made on the original patients, and a new group of seven cases has been investigated, throwing additional light on the syndrome, but a few words relating to the follow-up of the original cases may not be out of place. *Case 1:* This patient, who had become totally bedridden, steadily improved until the end of 1954, when he had virtually no disability; the plantar responses had become flexor, though there was still tendon areflexia. Unfortunately he died very suddenly, probably of coronary thrombosis, in January, 1955. *Case 2* is still under observation after five years; from being severely disabled he now walks normally and is able to hop on either foot; the areflexia remains but the electromyelographic changes are very much less marked. *Case 3* is still under observation after three years, and has no motor disability although when first seen he was bedridden. *Case 4* is now walking almost normally with no demonstrable weakness in the legs; the plantar responses are flexor and the knee-jerks have reappeared. Again the electromyelogram shows considerable improvement though it is still abnormal. *Case 5:* Unfortunately this patient cannot be traced.

In four of these five patients, therefore, there has been a striking recovery of power, with less obvious improvement in muscle-wasting, and they all demonstrate that weakness, areflexia, and extensor plantar responses are, in this condition, reversible. Since then seven additional patients have been seen who are probably suffering from a similar condition; reports of these cases are described in some detail.

## Reports of Further Cases

### Case 6

A man aged 68 was first seen in December, 1952. Three months previously glycosuria had been discovered and at the same time he had developed diffuse pain in the right leg and later wasting of the thigh, with increasing weakness. Although complete diabetic control was soon achieved his weakness increased. Weakness and wasting were much more pronounced in the thigh than in the calf, with absence of the knee-jerk and depression of the ankle-jerk. The C.S.F. protein content was 58 mg. per 100 ml. The electromyelogram of affected muscles showed profuse fibrillation activity at rest; the most severely involved muscles showed no motor-unit activity under voluntary control. The remainder showed discrete motor-unit activity on voluntary contraction, but the surviving motor units were of abnormally short duration and very small amplitude. These findings are suggestive of a peripheral nerve lesion as seen in "polyneuritis." Later the patient began to improve, his pain had disappeared by April, 1953, and the weakness largely so by June, 1954, by which time he was making no complaint, though there was still wasting of the right thigh muscles, with absence of the knee-jerk.

*Comment.*—The evidence for a cord lesion is not established in this patient, but widespread weakness and wasting of muscles in the absence of sensory loss makes a peripheral nerve lesion improbable and seems to take the pathology back at least as far as the anterior nerve roots. It remains, however, a painful but otherwise purely motor disorder associated with diabetes.

### Case 7

A man aged 57 was first seen in September, 1953, complaining of deadness and discomfort in the left hand, later the right hand, and then, with pain, the left foot. For three months there had been weakness and wasting of the muscles of the right hand, and the plantar responses were extensor. Although there were no relevant symptoms a glucose-tolerance test was carried out because both his mother and a sister were known diabetics. He was found to have a fasting blood sugar of 250 mg. per 100 ml. rising to 370 mg., with 5% glycosuria. The C.S.F. protein was 35 mg. per 100 ml. Full diabetic control was easily achieved, and he began to improve very quickly. When last seen in July, 1954, he had made a virtually complete recovery, though the left plantar response still appeared to be extensor. Unfortunately no electromyelogram was done.

*Comment.*—This example again has many features unlike the original description in that for the first time there was wasting of small hand muscles, the pain was of different distribution, and all the tendon reflexes were brisk. He was undoubtedly a diabetic, and there was a motor myelopathy which was reversed as soon as the diabetes was under control.

### Case 8

A man aged 63 was seen in November, 1954. There was a five-weeks history of weakness of the left leg, with falling, and he had lost 3 stone (19 kg.) in weight in the past year. For four months he had had constant, increasing, and diffuse abdominal pain, as well as pain in the lumbar region. Five months previously he had had a transient attack of right sciatic pain. Examination showed pronounced weakness

and wasting of the muscles of the left thigh with less marked change in the left calf, and loss of the left knee- and ankle-jerks; the right knee- and ankle-jerks were depressed. There was also marked weakness of the lower abdominal muscles and some weakness of the erector spinae. The glucose tolerance rose from 150 to 290 mg. per 100 ml., and was still 200 mg. at the end of two and a half hours, with glycosuria. The C.S.F. protein was 31 mg. per 100 ml. The E.M.G. of affected muscles showed decreased electrical activity on voluntary contraction; the more severely affected muscles showed discrete motor unit activity. The motor units were normal in appearance and there was no spontaneous activity.

He was treated with appropriate diet and insulin. The abdominal pain, however, increased and extensive investigation yielded negative results. He was submitted to laparotomy, but no visceral abnormality was found. He was given no other form of treatment, and when last seen in May, 1955, was making a steady recovery, so that practically all pain had gone, both from the leg and the abdomen, and all muscle power was returning. During the laparotomy naked-eye changes in the abdominal muscles were seen and a piece of the rectus abdominis was examined histologically; this showed only one out of several dozen muscle fibres to be normal, the others showing all stages of atrophy with increase in muscle nuclei and the formation of sarcophagic giant cells. It was thought that the inflammatory changes were secondary to neurogenic muscle degeneration.

*Comment.*—It will be seen that this patient closely resembles most of the previous patients, but again diabetes had not been previously suspected. Further, there seems to be strong evidence that the chronic abdominal pain and associated weakness and wasting of abdominal muscles were of cord and diabetic origin, and on this basis this case may well be unique. There can be no doubt about his steady improvement with diabetic control uncomplicated by any other form of therapy.

**Case 9**

A man aged 54 was first seen in November, 1954, when he had a ten-weeks history of pain in the right buttock and outer right thigh to the ankle, which was aggravated by walking. Weakness was almost limited to the right extensor hallucis longus, but the right knee-jerk and both ankle-jerks were absent and there was depression of the left knee-jerk. There was 1-in. (2.5-cm.) wasting of the right thigh and ½-in. (1.3-cm.) wasting of the right calf. *X*-ray examination showed considerable lumbar osteophytosis, and it was thought that this explained the syndrome; but when it was found that pain had not been relieved by strict rest further causes were sought. The C.S.F. protein was 20 mg. per 100 ml. Although glycosuria had not been detected, the glucose-tolerance test showed a fasting level of 106 mg. per 100 ml. rising to 228 mg., with slight glycosuria. The electromyelogram showed scanty fibrillation activity at rest in affected muscles. On voluntary contraction the electrical activity was decreased in amount and showed a tendency to discrete motor unit activity in places. Because the blood-sugar levels were not high he was treated by dietetic restriction alone, and when last seen in June, 1955, he was steadily improving and the pain had almost disappeared; the electromyelographic changes were then less marked.

*Comment.*—This patient resembles the last in that he had pain with weakness and wasting of muscles and areflexia, and that diabetes had previously been unsuspected. Some may feel that the diagnosis of diabetes is not established, but when a patient shows blood-sugar levels well over 150 mg. per 100 ml. two hours after taking 50 g. of glucose, presumably the ingestion of any average meal produces a similar effect, so that the central nervous system is being subjected several times a day to a metabolic disturbance that is well outside any normal variant. This man is also making a steady improvement as a result of dietetic restriction and with no other complicating therapy.

**Case 10**

A woman aged 47 was seen in April, 1955. She was known to have suffered from diabetes for ten years and had been on insulin throughout. She had often been in hypoglycaemic coma, and her diabetes had never been controlled. In 1951 she developed a tendency to fall, and weakness of the right foot was obvious in October, 1953. A calliper became necessary in November, 1954, and she felt that throughout the four years there had been slowly increasing weakness of both legs. Muscular wasting had been observed only of recent months. At no time had she complained of pain or paraesthesiae.

On examination there was diffuse but asymmetrical wasting with almost complete atonic paralysis of the right leg, and less marked weakness of the left. The right knee- and ankle-jerks were absent, the left knee-jerk was very brisk, and the left ankle-jerk was depressed. Owing to paralysis of the extensor hallucis longus it was impossible to assess the plantar responses. There was considerable contracture of both Achilles tendons. The electromyelogram showed evidence of denervation in the tibialis anticus, but almost no motor unit under voluntary control. The right quadriceps showed scanty fibrillation activity and occasional positive waves at rest. On voluntary contraction there was discrete motor unit activity, large in size, and voluntary contraction was initiated by these large units. Definite synchronization was detected, suggestive of a cord lesion. The C.S.F. protein content was 31 mg. per 100 ml. At the time of writing the patient was still in hospital and under treatment.

*Comment.*—It will be seen that this patient differed from the others in the complete absence of pain. Before being first referred she had been subjected to a biopsy from a leg muscle, and this showed changes similar to those seen in Case 8.

**Case 11**

A woman of 69 was seen in May, 1955. She was a known and uncontrolled diabetic and for five years had been on dietetic restriction only; at the time the diagnosis was established it was observed that the knee- and ankle-jerks were absent and she had probably had neurological symptoms for at least a year. Early in 1955 there had been a six-weeks period of diplopia. The patient said that throughout the five years she had tended to fall and had noticed a slowly progressive weakness of the legs, the left more than the right. She had observed wasting of the left leg for the past year, throughout which she had had to walk with a stick.

On examination there was diffuse wasting of the hypotonic left leg. Both knee- and ankle-jerks were absent; the right plantar response was extensor, but the left was not obtained because of paralysis of the extensor hallucis longus. Though an unreliable sensory witness, repeated testing made it certain that there was depression of vibration sense in the left leg and that it was absent in the left patella, but there was no other form of sensory loss. A glucose-tolerance test showed a fasting level of 220 mg. per 100 ml., rising to 330 mg., with glycosuria. The electromyelogram showed some fibrillation activity at rest in the affected muscles with occasional bursts of high-frequency discharge. Discrete motor unit activity was found on voluntary contraction with definite synchronization. This again was suggestive of a cord lesion. The C.S.F. protein was 50 mg. per 100 ml. The patient was still in hospital at the time of writing.

*Comment.*—It will be seen that this patient differed from the original group in that at no time was there any complaint of pain, the spinal fluid protein content was within normal limits, and there was slight sensory loss. It should again be emphasized that the diabetes had never been controlled during the past five years.

**Case 12**

A man aged 69 was first seen in May, 1955. There was a three-months history of progressive weakness, wasting, numbness, and pain in the feet. On examination there was

considerable wasting of the legs, the left more than the right, with tendon areflexia. There was marked wasting of the left gluteus maximus. He was a poor sensory witness and there was doubtful impairment of vibration sensation below the knees, but certainly no other form of sensory loss. The plantar responses were flexor. He was found to have marked glycosuria, and a glucose-tolerance test showed a fasting level of 270 mg. per 100 ml., rising to 400 mg. The C.S.F. protein was 29 mg. per 100 ml. The electromyelogram showed profuse fibrillation activity in the affected muscles at rest, and a much-decreased but well-sustained pattern of motor unit activity on voluntary contraction, suggesting a lesion in the peripheral part of the lower motor neurone.

*Comment.*—This is another example of a motor diabetic syndrome with little evidence of sensory loss and with no unequivocal evidence of a cord lesion. The patient was still under observation at the time of writing.

## Discussion

If it be accepted that 12 patients are suffering from a neurological syndrome determined by uncontrolled diabetes, the total clinical picture would seem to be different from that visualized in 1953. It is still true to say that the most usual features are diffuse pain, weakness, wasting, and areflexia, usually asymmetrical and limited to the legs. Less constant features are extensor plantar responses and a raised protein content of the C.S.F. Electromyelographic changes are not always similar; they often suggest a cord lesion, but sometimes the changes appear to be of peripheral origin. It would also seem clear that the lesion is not limited to the lumbar cord and may involve cervical or dorsal segments. Because of the variable findings "diabetic amyotrophy" rather than myelopathy is perhaps the most suitable designation.

With regard to causation, these patients only serve to confirm the oft-repeated views of the past—namely, that neurological complications of diabetes of any form are determined by incomplete control of the diabetes and that they result from the effects of disordered glucose metabolism on the nervous system. It is now generally held that vitamin deficiency plays no part in the production of these complications and there is nothing to suggest that it operated in these patients; they have shown no clear evidence of arteriosclerosis, and it would seem unlikely that arteriosclerotic changes in the cord or peripheral nerves have to be considered. Since the metabolism of the nervous system is largely that of glucose it is not surprising that disturbances of glucose metabolism often result in neurological disorders. In this connexion it is interesting that cord changes are known to result from hypoglycaemia, though in the present state of our knowledge this seems to be rare. An excellent example has, however, been described by Williams (1955) in a patient who showed marked wasting of the small hand muscles, with fasciculation of thigh muscles and, to a less extent, of muscles below the knee; there were no notable reflex changes and no sensory loss, but the syndrome was associated with cerebral hypoglycaemic episodes and the neurological picture rapidly improved after the surgical removal of an islet adenoma of the pancreas.

Since 12 examples have come to my notice in a five-year period it would seem that diabetic amyotrophy is by no means rare, and, of these, only three were sent to me with this diagnosis already under consideration. The reasons why the syndrome has been, and is still being, overlooked are no doubt multiple. In the first place, most of these patients develop the syndrome at a time when they are known to be diabetics. Because the neurological picture does not conform to the well-known and largely sensory neuropathy the physician makes another diagnosis and considers the neurological picture to be coincidental; the diagnoses usually made are sciatica or some other complication of lumbar osteophytosis, or motor neurone disease. Conversely, the patient presenting first to the neurologist when diabetes has not been suspected may also be given an inaccurate diagnostic label whilst his diabetes is completely overlooked, as could easily have happened in Cases 7, 8, and 9. So long as diabetes is given no further aetiological consideration on the basis of an occasional sugar-free specimen of urine these patients will continue to be missed.

From personal experience it seems that the most severe and totally crippling disability arising from diabetic amyotrophy is always potentially reversible. I am satisfied that the only way to achieve success is by total diabetic control, with the patient at first in hospital. Active physiotherapy, in the form of appropriate exercises, together with the use of callipers and crutches, may play some part in hastening functional recovery, and the treatment of tendon contractures may be called for. Whether the muscular wasting is always reversible has yet to be decided. The position of electromyography is also uncertain, and some may think it is very largely an academic problem. All affected muscles in the above patients have shown electromyographic abnormalities, but the pattern of these changes has shown wide variation. In some of the cases where the electromyelographic changes suggested a cord origin the clinical findings have been unequivocally those of a myelopathy; but in others this has not been so, and it would be true to say that the distribution of weakness, wasting, and areflexia seems to follow a similar pattern no matter what the nature of the electromyographic change.

Since it is generally accepted that diabetic neuropathy is usually purely sensory and is determined by peripheral nerve changes only, it may equally well be true that diabetes can produce changes limited to the motor fibres of peripheral nerves. But it would seem that diabetic amyotrophy is always a reversible process no matter where the anatomical disturbance appears to be. Although diabetes may determine changes in the spinal cord it may presumably result in changes in the peripheral nerves of the same patient at the same time. Sensory loss has been largely absent in this group, but the finding of sensory loss in no way vitiates the diagnosis of "diabetic amyotrophy."

## Summary

Twelve patients are described, showing a syndrome which includes weakness and wasting of muscles with tendon areflexia, all associated with frank diabetes or at least with impaired glucose tolerance.

There is evidence that some of these cases result from a myelopathy and that changes may occur at any cord level, though they are most commonly seen in the lumbar region.

Pain of a similar distribution to the amyotrophy is a frequent though not constant feature.

The protein content of the C.S.F. may be normal or raised.

Affected muscles always show electromyographic changes, though of varying character.

At the present time "diabetic amyotrophy" would appear to be the best term to apply to the syndrome.

Diabetic amyotrophy is the result of uncontrolled diabetes and is probably always reversible by full diabetic control.

I wish to thank Dr. J. R. H. Towers, the Medical Professorial Unit, and Dr. J. A. Price, who kindly referred Cases 10, 11, and 12. All the electromyograms were carried out by Dr. D. Taverner.

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# USE OF SCHULTZ-DALE TEST FOR DETECTION OF SPECIFIC ANTIGEN IN SERA OF PATIENTS WITH CARCINOMA

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Early diagnosis is still the keystone for effective treatment of cancer in the majority of cases. It is therefore not surprising to find a very long list of attempts at diagnostic procedures for cancer. Homburger (1950) lists a number of these tests, including those with and without some established value. The great majority of these tests, however, are not specific and have failed to fulfil the requirements put up by Dunn and Greenhouse (1951) of no more than 10% false negatives and not more than 5% false positives.

Although the morphological methods used, including the comparatively new method of Papanicolaou, still provide the basis of diagnosis, they have, as Homburger points out, many drawbacks. Apart from the necessity for highly skilled personnel, the Papanicolaou technique is useful only in those lesions where the cells can be scraped from the surface, or that are freely accessible to liquids which can wash away desquamated cells and bring them within the reach of the examiner.

The need is therefore great for a specific test which could utilize a more general common characteristic of neoplasms, and which could be applied to the blood or body secretions, for the detection of all types or any given type of cancer.

The utilization of immunological procedures to detect specific changes in the blood of patients with cancer would seem to be promising in its approach to the problem. Numerous tests based on immunological reactions have been described, but have not been proved of practical value. A number of these tests have been listed (Homburger, 1950; and U.S. Public Health Service, 1951, 1953). The immunological blood tests described are all concerned with detection of antibodies.

It has been found by Schultz (1910) and Dale (1913) that when the sensitized guinea-pig intestine or uterus is removed from the body and suspended in oxygenated Ringer's solution, maximal contraction will occur on exposure to even small amounts of antigen. Using the Schultz–Dale reaction, Makari (1953) was able to detect rickettsial antigen in egg yolk and cotton-rat liver. Similarly, Makari and Mirick (1955) were able to detect a soluble antigen in sera of patients with infective hepatitis and homologous serum jaundice. Using the same method, Makari (1955a, 1955b) described the presence of a soluble carcinoma antigen.

The present preliminary report concerns the use of the Schultz–Dale technique for the detection of a soluble antigen in the sera of patients with carcinoma, and the possible application of this finding for diagnosis of carcinoma in man. A more detailed report will be published elsewhere.

## Materials and Methods

Virgin female guinea-pigs weighing about 300 to 400 g. were immunized to antigens from carcinomatous tissues by the help of Freund's adjuvants. After four weeks they were killed by a blow on the head, and their uterine horns were removed and tested in a modified Schultz–Dale apparatus shown in Fig. 1.

The Tyrode solution used was the one suggested by Coulson *et al.* (1943), with the calcium chloride content diminished to 0.05 g. per litre. A mixture of 95% oxygen and 5% carbon dioxide was bubbled through. Air has proved satisfactory in more recent work. Recordings were done with ink on B.M.R. calibrated paper mounted on rotating kymographs. A run lasted for five minutes, and covered a total of 10 cm. on the drum.

Before the addition of the serum to be tested, the horn was allowed to remain in the Schultz–Dale bath long enough

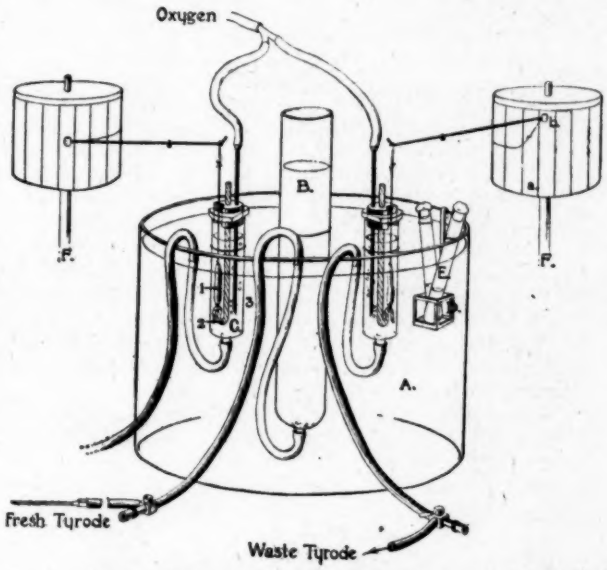


FIG. 1.—Schultz–Dale apparatus as modified for use in this work. A = Water-bath at 37.5° C. B = Tyrode reservoir. C = Schultz–Dale bath. (1) Uterine horn. (2) Glass rod for attachment of lower end of horn. (3) Needle for bubbling 95% oxygen and 5% carbon dioxide. D = Test-tube holder. E = Sterile test-tubes with serum or plasma to be tested. F = Kymographs. (*a*) B.M.R. paper. (*b*) B.M.R. ink-tip.

to ensure complete relaxation. A horn from an unsensitized normal guinea-pig was used as a control. Several antigens were used to immunize these guinea-pigs: *Antigen A* was prepared by homogenization in a Waring blender of carcinomatous tissue under sterile precautions, which was then made a 20% emulsion in normal saline. *Antigen B* was prepared from the HeLa strain of cancer cells grown in tissue culture in Dr. Gey's laboratory (Gey and Gey, 1949; Gey *et al.*, 1952). *Antigen C* was the supernatant obtained after centrifugation of antigen A at 3,200 r.p.m., equivalent to an R.C.F. of 1.5 kg. per g. Antigen C was further fractionated by centrifugation to Sediment II, obtained between 3,200 and 4,000 r.p.m., equivalent to an R.C.F. of 2.3 kg. per g., and Sediment III, between 4,000 and 10,000 r.p.m., equivalent to an R.C.F. of 10.3 kg. per g.

The testing procedure was started with the addition of 0.5 ml. of normal Group O plasma to the Schultz–Dale bath, which did not result in contraction of the normal horn, but caused a specific contraction of the sensitized horn, due to a common component between the cancer antigens and normal Group O plasma. Further additions of normal Group O blood in 0.5-ml. amounts were made until the horns did not record any contraction on contact with the Group O plasma for five minutes (one run), indicating complete desensitization of the sensitized horns to antigens in normal blood.

After each addition of serum, the Tyrode solution in the Schultz–Dale bath was changed a sufficient number of times (three or four) to allow the return of the kymograph reading to the baseline.

After desensitization to Group O was accomplished, any serum or plasma which gave a positive reaction in the sensitized horn, but not in the normal horn, was considered a positive reaction. Any serum which caused a contraction of the normal horn could not be evaluated. Only contractions which were at least one-fifth as strong as that produced by 10 gamma of histamine base were considered as significant. The record of a typical experiment is shown in Fig. 2.

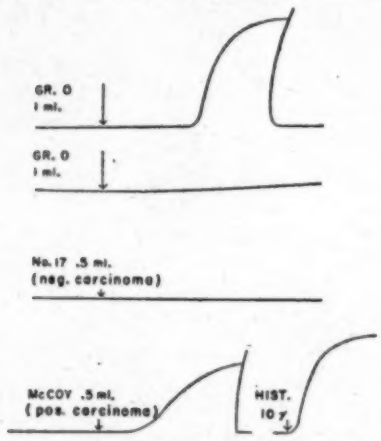


FIG. 2.—Record of a typical experiment on guinea-pig 56, Group 20, actively sensitized to FrO antigen C on November 12, 1953, and sacrificed a month later.

Serum obtained from guinea-pigs or rabbits four to six weeks after primary immunization, or one to two weeks after secondary immunization, was used for passive sensitization. Normal uterine horns were passively sensitized by contact with such serum for one hour at 4° C. Horns passively sensitized by this treatment may be used in the Schultz–Dale bath in the same way as the actively sensitized ones.

The sera tested were collected from patients at the Johns Hopkins and Baltimore City Hospitals. The diagnoses were as follows: definite carcinoma, questionable carcinoma (including hyperplasias), other malignant or benign tumours, and non-neoplastic diseases. The cases of carcinoma or other tumours were divided into untreated cases and those which had received radiotherapy and/or surgery. Presumably normal individuals from the Cancer Detection Clinic at the Johns Hopkins Hospital were also studied.

Individuals of both sexes were used throughout the study, and the age range was 35 to 65 years. A total of more than 1,000 sera were studied from 654 persons by this test. An additional 47 patients were studied for the presence of a pressor substance only, and an additional six for platelet effect. Reproducibility of the test was studied by means of plasma pooled from three cases of carcinoma or plasma pooled from three normal Group O individuals.

The conditions under which the serum was collected and stored had considerable influence on the outcome of the test, and this phase of the investigation will be described in detail elsewhere. Unless otherwise specified, serum was stored for 24 hours at 4° C. before being used. If not used immediately, further storage was at −40° C.

### Sensitivity and Specificity of Test as Related to Immunizing Antigen

The results of the Schultz–Dale test on sera from 517 individuals are shown in Table I and Fig. 3.

With antigens A and B, active sensitization resulted in a positive test in 59 out of 70 (84%) cases of untreated carcinoma, and passive sensitization yielded a positive result in 18 out of 21 (86%) such cases. The incidence of positive reactions in questionable cancer cases was 11 out of 18 with active sensitization, and five out of five with passive sensitization. Two out of 10 cases of tumour other than carcinoma gave positive reactions with active sensitization and two out of four with passive sensitization.

The incidence of positive reactions among individuals from the Cancer Detection Clinic was 5% (6 out of 111) with active sensitization, and 4% (1 out of 26) with passive sensitization. In cases with other diseases 19 out of 23 (82%) were positive with active sensitization, and 8 out of 25 (32%) were positive with passive sensitization.

When antigen C was used—that is, the antigen with small-sized particles—the sensitivity and specificity of the test were

TABLE I.—*Distribution of Positive Reactors to Schultz–Dale Test among Untreated Carcinoma Cases; Cases with Questionable Carcinoma, other Tumours, and other Diseases; and Presumed Normals*

| Source of Antigen | Type of Antigen Used | Type of Sensitization | Positive Carcinoma | | Questionable Carcinoma | | Other Tumours | | Other Diseases | | Presumed* Normals | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total Cases | Positive Cases | Total Cases | Positive Cases | Total Cases | Positive Cases | Total Cases | Positive Cases | Total Cases | Positive Cases |
| Carcinoma of ovary H. S. or HeLa strain tissue culture | Antigens A and B (large- and small-sized particles) | Active | 70 | 59 (84%) | 18 | 11 (61%) | 10 | 2 (20%) | 23 | 19 (82%) | 111 | 6 (5%) |
| | | Passive | 21 | 18 (86%) | 5 | 5 (100%) | 4 | 2 (50%) | 25 | 8 (32%) | 26 | 1 (4%) |
| Carcinoma of sigmoid C. H. or Carcinoma of bronchus M. J. | Antigen C (small-sized particles) | Active | 64 | 62 (96·8%) | 8 | 3 (37·5%) | 9 | 1 (11%) | 123 | 6 (4·8%) | — | — |

* Individuals tested from the Cancer Detection Clinic at the Johns Hopkins Hospital.

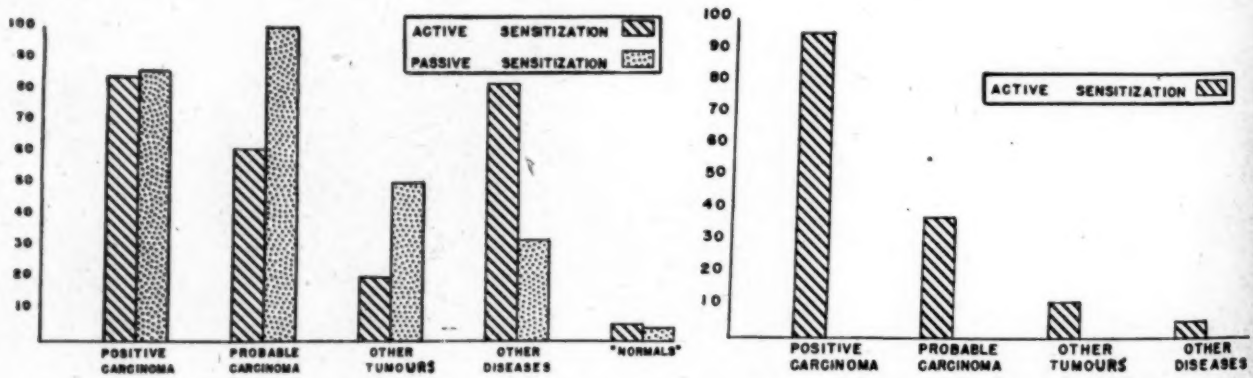


FIG. 3.—Percentage distribution of positive reactors to the Schultz–Dale test in 313 cases where antigens A and B were used for sensitization (left), and in 204 cases where antigen C with small-sized particles was used (right).

greatly increased. With the active sensitization technique the incidence of positive reactors in the definite carcinoma cases was 62 out of 64 (96.8%); in the questionable cancer cases, 3 out of 8; in other tumours, 1 out of 9; and in other diseases, 6 out of 123 (4.8%).

*Untreated Carcinoma.*—Results obtained with active sensitization in the 134 patients with untreated carcinoma are listed in Table II with regard to the site of the carcinomatous process. It is apparent that nearly all carcinomas

TABLE II.—*Distribution of Sites of Origin in 134 Untreated Carcinoma Cases Tested by Active Sensitization with Schultz-Dale Test*

| Source of Carcinoma | Antigens A and B (H. S. and HeLa Strain) | | Antigen C (C. H. or M. J.) | |
|---|---|---|---|---|
| | Total | Correct Diagnosis | Total | Correct Diagnosis |
| Abdominal cavity | — | — | 4 | 4 |
| Bladder | 6 | 6 | 1 | 1 |
| Bone | 1 | 1 | — | — |
| Brain | — | — | 2 | 2 |
| Breast | 1 | 1 | 4 | 4 |
| Bronchi | — | — | 2 | 2 |
| Cervix | 7 | 7 | 1 | 1 |
| Colon | 1 | 1 | 1 | 1 |
| Generalized (metastasis) | 6 | 3 | 9 | 9 |
| Larynx | — | — | 4 | 4 |
| Lung | 1 | 0 | 4 | 4 |
| Mediastinum | — | — | 1 | 1 |
| Neck | — | — | 1 | 1 |
| Oesophagus | 2 | 2 | 2 | 2 |
| Ovary | 1 | 1 | — | — |
| Pancreas | 1 | 1 | 2 | 2 |
| Penis | 1 | 1 | — | — |
| Pharynx | — | — | 2 | 0 |
| Prostate | 15 | 10 | 1 | 1 |
| Recurrent | 1 | 1 | 1 | 1 |
| Rectum | — | — | 1 | 1 |
| Site not recorded | 15 | 14 | 16 | 16 |
| Skin | 1 | 1 | — | — |
| Stomach | 3 | 3 | 2 | 2 |
| Testes | — | — | 1 | 1 |
| Tongue | 4 | 4 | — | — |
| Thyroid | 2 | 1 | — | — |
| Uterus | 1 | 1 | 2 | 2 |
| | 70 | 59 (84%) | 64 | 62 (96·8%) |

tested from the 28 sites listed have antigens in common with the carcinomas used in preparing the antigens employed for sensitization. From these findings one might reasonably postulate the presence of common antigens among all carcinomas. Such a common antigenicity would provide a rational basis for immunological detection of carcinomas, using a single antigen. It will be noted that the proportion of false negatives was largest with antigen B prepared from the HeLa strain of carcinoma. Of the false negatives obtained with antigen B, 8 out of 11 were from patients with carcinomas of the prostate or metastatic carcinoma. These findings suggest a possible loss of antigenicity through adaptation of the HeLa strain to its abnormal environment in tissue culture. This loss may selectively involve one or more antigens, and may be related to the capacity of tumour cells to metastasize.* The two cases giving false-negative results with antigen C were both carcinoma of the pharynx, a finding for which no explanation is apparent.

*Carcinoma Treated with Surgery or Radiotherapy.*—When guinea-pigs actively sensitized to antigens A and B were used to test sera from surgically treated carcinoma patients during their first post-operative week, four out of six gave positive results, and one out of three gave a positive reaction with sera obtained after the first week of operation. With antigen C one out of four gave a positive reaction with sera taken in the first post-operative week. With sera from patients who had received radiotherapy within the previous week, four out of four cases were positive. In another case the test was negative seven weeks after radiotherapy. The number of cases studied following therapy is too small for any evaluation.

*Other Tumours.*—In Table III are shown results obtained with 19 cases having tumours other than carcinoma. Two cases of sarcoma, mentioned below in the questionable group and giving negative results, are not included. Of the two patients showing positive results with antigens A and B, one had a melanoma and the other a seminoma.† The negative

TABLE III.—*Incidence of Positive Reactors to Carcinoma Antigens in the Schultz-Dale Test in Other Tumours than Carcinoma*

| Type of Tumour | Antigens A and B | | Antigen C | |
|---|---|---|---|---|
| | Total | Positive | Total | Positive |
| Carotid tumour | — | — | 1 | 0 |
| Hodgkin's disease | 1 | 0 | 3 | 0 |
| ,, sarcoma | 1 | 0 | — | — |
| Leukaemia | 1 | 0 | 2 | 0 |
| Lymphoma | 1 | 0 | — | — |
| Lymphosarcoma | 1 | 0 | — | — |
| Melanoma | 2 | 1 | 1 | 1 |
| Myoma | — | — | 1 | 0 |
| Reticulum-cell sarcoma | 1 | 0 | — | — |
| Sarcoma | 1 | 0 | 1 | 0 |
| Seminoma | 1 | 1 | — | — |
| | 10 | 2 | 9 | 1 |

cases included four sarcomas, a lymphoma, a case of leukaemia, and a case of Hodgkin's disease. With antigen C only one of nine cases was positive, and this was also a melanoma. The negatives included two leukaemias, three cases of Hodgkin's disease, one sarcoma, one carotid body tumour, and one uterine myoma. It is of interest to note that of the three melanomas studied two were positive, indicating a common antigenic component perhaps with carcinoma, and so was the case of seminoma studied. The cases of sarcoma, Hodgkin's disease, and leukaemia studied did not show any common antigenicity with the carcinoma antigens used, as evidenced by the negative reactions obtained.

*Other Diseases.*—With guinea-pigs actively sensitized to antigens A and B, 19 out of 23 cases of non-neoplastic disease gave positive tests. Since sera from the positive cases were not tested with unsensitized horns, it is not apparent whether positives were due to a pressor substance and/or a common antigen.

Of the 123 cases studied with guinea-pigs actively sensitized to antigen C, 6 gave positive results when tested with unsensitized horns, indicating the presence of a pressor substance, and thus could not be evaluated.

*Cancer Detection Clinic.*—A total of 111 apparently healthy adults of both sexes were studied by the active sensitization method with antigens A and B. Of these, six were positive reactors. These six were also shown to have pressor substances when tested with unsensitized horns. When these cases were being studied the thermolability of this pressor substance and the use of platelet intact plasma had not been established. It was therefore not known whether or not these positive results were false positives in the usual sense.

### Follow-up of Cases with Clinical Diagnosis of Questionable Carcinoma

The cases in this group were followed for a period of one year. Of the 26 cases, the 9 in which a definite pathological diagnosis was obtained at necropsy or by biopsy are reported in Table IV.

On subsequent pathological examination a diagnosis of carcinoma was not obtained in any of the four cases showing a negative reaction, the pathological diagnoses being fat necrosis, lupus erythematosus, haemangiosarcoma, and spindle-cell lipo-fibrosarcoma.

Of the five cases with a positive reaction, four proved to be definite carcinoma. The fifth case, J. C., had a recurrent papilloma of the bladder, which was found at operation a day later to be penetrating the bladder wall, suggesting beyond doubt its carcinomatous nature.

*After this article was prepared, Dr. H. N. Green's article (*British Medical Journal*, 1954, **2**, 1374) on an immunological concept of cancer was noted, which supports this idea.

†While the question of melanoma is still a debatable issue, the great majority of workers feel that since the seminoma is a tumour of germinal epithelium it is best grouped under carcinoma.

TABLE IV.—*Follow-up of Cases with Questionable Clinical Diagnosis of Carcinoma*

| Initials | Diagnosis at Time of Testing | Result of Test | Final Diagnosis by Biopsy or Necropsy | Interval Between Test and Definite Pathological Diagnosis in Days |
|---|---|---|---|---|
| M. C. .. | ? Carcinoma of bladder | + | Carcinoma (bladder) | 28 |
| A. G. .. | ? Carcinoma of pancreas | + | Carcinoma (head of pancreas) | 10 |
| J. S. .. | ? Carcinoma of lung | + | Undifferentiated carcinoma of lung | 4 |
| G. M. .. | ? Carcinoma of gums (recurrent) | + | Extensive carcinoma (recurrent) | 151 |
| J. C. .. | Papilloma ? carcinoma of bladder | + | Papillary squamous-cell tumour with invasion of bladder wall | 1 |
| A. B. .. | ? Carcinoma of breast | − | Fat necrosis (no carcinoma) | 14 |
| A. R. .. | ? Carcinoma of lymph node | − | Lupus erythematosus (no carcinoma) | 20 |
| J. Y. .. | ? Carcinoma of stomach | − | Haemangiosarcoma (tail of pancreas) | 56 |
| E. C. .. | ? Carcinoma of stomach (history of carcinoma of cervix—well treated) | − | Spindle-cell lipofibrosarcoma | 1 |

### Localization of Activity in Relation to Particle Size of Antigen

When the differential centrifugation procedures described under "methods" were used the following results pertaining to the sensitivity and specificity of the different fractions were obtained.

Sediment I had no antigenicity, while the final supernatant (III) had very good antigenicity but poor specificity. Supernatant I possessed relatively poor antigenicity but good specificity. Both Sediments II and III had very good antigenicity, but Sediment II had the better specificity. Furthermore, in contrast to Sediment III, Sediment II did not lose its antigenicity on storage in the deep freeze at −20° C.

### Variables Introduced by Different Methods of Treatment of Serum

We used 114 sera from cases of untreated carcinoma and those with other diseases. Three cases of carcinoma receiving previous treatment were excluded. The sera were given numbers unknown to the person operating the test. The results of these tests, shown in Table V, indicate the importance of controlling certain variables in the treatment of sera to be tested, to ensure accuracy of results and to avoid false-positive or false-negative reactions.

It is apparent from these experiments that two factors are of paramount importance in determining the incidence of false positives and false negatives: (1) The particle size of antigen used in the sensitization of guinea-pigs. (2) The type of treatment which the serum undergoes—mainly storage period at 4° C., and −20° C. where antigenicity may be partially lost and where a non-specific pressor substance, possibly resulting from slow disintegration of the platelets, may be formed.* This pressor substance, due to platelet destruction, was further proved in other experiments to be described elsewhere. Storage at −40° C. did not result in a loss of antigenicity nor in the production of false-positive reactions for as long as 150 days. Routinely, as mentioned before, the serum was left for one day at 4° C. and then either tested or kept at −40° C. and then tested.

Excluding Group I, where large-sized particles were used, it will be seen that the percentage of correct diagnosis was inversely proportional to the period of storage of serum at 4° C. and at −20° C. before testing.

Another experiment was done to compare the incidence of false-positive reactions in routinely stored sera left overnight in the ice chest at 4° C., which would be comparable to the other group studied and referred to under "sensitivity and specificity of test as related to immunizing antigen."

*At the M. D. Anderson Hospital and Tumor Institute we have been using routinely drawn blood in heparinized syringes into lustroid tubes and have since rarely noticed this pressor effect.

Forty-seven sera from patients with other than neoplastic diseases were obtained from the chemistry laboratory of the Johns Hopkins Hospital. These were kept overnight at 40° C. in the same way as the routinely stored sera, and then tested for non-specific pressor effect on non-sensitized uterine horns. Two out of 47 gave false-positive reactions, an incidence of 4.2%.

### Reproducibility of Test

Platelet-intact plasmas from three Group O normal blood donors were added together to make a negative carcinoma pool, while platelet-intact plasmas from three cases with untreated carcinoma were also added together to make a positive carcinoma pool. Plasma was then pipetted in 2-ml. amounts into 50 sterile test-tubes and given numbers unknown to the person doing the test. Seven were from the carcinoma-positive pool and the other 43 were from the normal Group O pool: all of the positives and all of the negatives were correctly diagnosed.

Reproducibility of this test was also studied in another way. Sera from 15 untreated carcinoma cases were tested by "active sensitization" to antigens A and B repeatedly for a total of 35 times. In the interval after testing, these sera were kept frozen at −40° C. In all 35 tests a positive reaction was obtained. Similarly, 3 sera from 31 untreated carcinoma cases were studied by "active sensitization" to antigen C for a total of 77 times over a period of two months of storage at −40° C. In 75 of the 77 tests the reaction was positive.

A case of cancer of the lung shows this point. The test done on the patient's serum stored at −40° C. showed consistently positive results when tested 11 times during a period of two months and compared very favourably with a fresh sample of serum obtained two months later and tested four times. However, this stored serum when tested on the tenth and eleventh time, although still positive, was getting weaker as compared with the previous tests and also with tests on the fresh serum. It was therefore possible to keep in this way a positive serum control from a carcinoma patient ready at all times for testing.

### Discussion

The utilization of immunological techniques for diagnostic purposes has been limited in the past to detection of antibodies, a procedure inherited from the earlier days of bacteriology that has proved very fruitful in many bacterial diseases, but less so in parasitic and neoplastic diseases, and in many diseases of viral origin. The detection of antibodies necessitates that the host, in response to the presence of antigens, react by forming detectable antibodies in all cases, a step which may or may not take place in all patients, and therefore may account for the failures in the past attempts to detect antibodies constantly in animals or in patients with cancer. By looking for antigens instead of antibodies this difficulty is removed.

The problem of how best to detect these soluble antigens in the blood presents a number of difficulties. With the immunological techniques as normally employed, such as precipitation, agglutination, or complement fixation, univalent antibodies—that is, those antibodies with but one reactive group per antibody molecule—are not detectable. It has been found that an antibody which reacts demonstrably but does not precipitate may be present in some sera and that such antibody might be able to sensitize (Boyd, 1947). Furthermore, differences in the ability of antibodies of different species to fix complement or to sensitize guinea-pigs have been described by Kabat and Mayer (1948). Kabat and Landow (1942) have reported that an isolated guinea-pig uterus will contract even though containing amounts of antibody nitrogen not exceeding 0.01 μg. This reaction is therefore much more sensitive than any *in vitro* immunological method.

These considerations make the Schultz–Dale the test of choice for detection of antigens, not only for its technical soundness as a specific immunological test but also for its great sensitivity.

TABLE V.—*Variables Introduced by Different Methods of Treatment of Serum and by Particle Size of Antigen*

| Unknown Group No. | Treatment of Serum Storage in Days | | | Type of Sensitization | Total No. Sera Tested | Result of Test | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | +Clot 4° C. | −Clot 4° C. | −Clot −20° C. | | | Correct Pos. | Correct Neg. | False Pos. | False Neg. | Correct | |
| I | 1 | — | 5 | Passive | 25 | 6/11 | 6/14 | 8/14 | 5/11 | 48% (12/25) | Use of large-sized particle antigen blamed for failure |
| II | 1 | 30 | — | Active | 18 | 4/9 | 1/5 | 4/5 | 5/9 | 36% (5/14) | Prolonged storage of serum at 4° C. blamed for failure |
| III | 4 | 10 | 25 | ,, | 38 | 11/19 | 11/19 | 8/19 | 8/19 | 58% (22/38) | Prolonged storage at 4° C. and −20° C. blamed for failure |
| IV | 1 | 2 | — | ,, | 16 | 7/7 | 7/9 | 2/9 | 0/7 | 88% (14/16) | Result good, but use of inert antigen cut down on specificity |
| V | 1 | 7 | — | ,, | 17 | 8/8 | 8/9 | 1/9 | 0/9 | 94% (16/17) | Results excellent, but tests all weak owing to partial loss of antigenicity from storage at 4° C. |

The results of tests described here on 707 sera from patients at Johns Hopkins and Baltimore City Hospitals show the value of this approach in the detection of a soluble antigen from the blood of patients with carcinoma.

The results obtained when the test is done under the best conditions yet developed shows a very high specificity of 96.8%, with a false positivity of 4.7 to 5% in cases with other diseases or persons coming to the Cancer Detection Clinic respectively. These cases have not been followed long enough to rule out the possibility of their having real positive reactions and may not represent false positives in the real sense. These figures are still in conformity with the requirements as put up by Dunn and Greenhouse (1951).

It should be emphasized here that this antigen is a common antigen for all carcinomas, as evidenced by the fact that it is present in carcinomatous tissues and in bloods from untreated carcinoma patients regardless of site of origin and type of carcinoma. This fact adds a lot to the practical usefulness of such an approach as a diagnostic procedure. Moreover, it should also be emphasized that this antigen present in carcinomas does not seem to show common antigenicity with sarcomas, Hodgkin's disease, leukaemia, or benign tumours studied. It has, however, common antigenic components with two of the three melanomas and with the one seminoma case studied.

This test, however, like many biological tests, has a number of pitfalls which should be carefully avoided if the best results are to be obtained. As already shown, the best antigen to be used for immunization should include only those particles of a small size. The best of these seem to be Sediment II and Sediment III. Inclusion of large-sized particles or the remainder of the supernatant increases false-positive reactions. Furthermore, it is best to use heparinized plasma drawn the same day or serum after 24 hours' storage at −4° C.

Passive as well as active sensitization could be used. Passive sensitization might provide a much more practical way, since serum with high antibody content could be lyophilized and kept available in the laboratory for such testing at any time. By use of the passive sensitization technique, methods might be developed for standardization of antibody titre in the guinea-pig or rabbit serum, and consequently that coating the uterine horn.

Of great interest are the results of the nine cases with a questionable clinical diagnosis of cancer, which were followed up to one year for pathological diagnosis, and which revealed the high specificity and accuracy of the test. This was apparent not only in the elimination of other tumours, such as sarcomas, and other conditions, such as lupus and fat necrosis, but also in the early detection of positive cancer cases in a period varying from 4 to 151 days before definite clinical and pathological diagnosis was made. Although these cases are too few to draw any conclusions from, they point to a very fundamental issue, which will be evaluated in subsequent work.

G. M., a case of squamous-cell carcinoma of the gums with invasion of the mandible, illustrates this point. She was treated by resection during the first operation on September 30, 1952, when a definite diagnosis of squamous-cell carcinoma, grade I, was made. The test was made on February 1, 1953, and was positive. A second operation was done on February 26, 1953. The surgeon thought then that all the cancer tissue had been previously removed by composite resection of the lesion of the cheek, and during this time skin grafts were done. The patient became progressively worse, however, with very extensive recurrent carcinoma, involving the whole left side of the face, with multiple draining sinuses, and died on August 9, 1953. It is to be noted that the test was positive about a month before the second operation, when the patient was thought, on clinical grounds, to be free of carcinoma. Six months after the positive test, and five months after she was pronounced clinically free, the patient died with extensive carcinoma.

## Summary

The detection of a specific soluble antigen in the sera of carcinoma patients, by use of the Schultz–Dale test on actively or passively sensitized uterine horns, is described. Under the best conditions yet found—that is, when the serum or plasma is used fresh or after storage at −40° C., or where platelet-intact or platelet-free plasma is used, and when the sensitizing antigen is of small particle size—this test shows a high degree of specificity and sensitivity, it being positive in 96.8% of carcinoma cases, in 4.8% of other diseases, and in 4 to 5% among cases from the Cancer Detection Clinic.

Further work is in progress at the University of Texas, M. D. Anderson Hospital and Tumor Institute, to help standardize this test and to evaluate on a larger scale the possibility of its use as an early diagnostic aid in individual cases and in the screening of carcinoma in the general population.

I wish to thank Dr. George S. Mirick, Associate Professor of Medicine at Johns Hopkins Hospital, for his advice and help and for making available the necessary laboratory facilities; Dr. George O. Gey for making available the HeLa strain from his tissue-culture laboratories; Dr. Bernard C. Brack for permission to obtain blood from patients coming to the Cancer Detection Clinic; Drs. E. Staten Wynne and R. W. Cumley for help in editing the manuscript; and Mrs. Marie Maselbas and Mr. John Lockner for valuable technical assistance.

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# PARATYPHOID FEVER ASSOCIATED WITH CHINESE FROZEN WHOLE EGG

## OUTBREAKS IN TWO BAKERIES

BY

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For many years there have been outbreaks of paratyphoid fever associated with the consumption of imitation cream cakes and other confectionery made in commercial bakeries. One suspected means of entry of the paratyphoid bacillus into these bakeries has been contaminated products in common use (Cockburn *et al.*, 1951 ; Thomson, 1953). In 1954 two of us investigated a series of outbreaks of paratyphoid fever associated with bakeries where one small batch of Chinese frozen whole egg, used in all the bakeries concerned, was thought to have been contaminated, but where only a small amount was available for examination (Newell, 1955 ; Smith and Hobbs, 1955 ; Newell *et al.*, 1955). Various salmonellae were found, but not *Salmonella paratyphi B*.

In the present report are recorded two outbreaks of paratyphoid fever in August, 1955, one in the Worthing area and the other in the Weymouth area ; bakery products were suspected of being directly responsible for the infection, and a batch of Chinese frozen whole egg used in the two bakeries appeared, on epidemiological grounds, to be the source of contamination. The epidemiological observations were confirmed by the isolation of the same phage type of *Salm. paratyphi B* from unopened cans of the egg, from some of the bakery staff, and from the patients.

### Worthing Outbreak

Fourteen patients with an illness of the enteric fever type were found to be excreting *Salm. paratyphi B* phage type 3a ; two of them were also found to be excreting *Salmonella thompson*. These illnesses began between August 7 and 21. Two patients had first had a gastro-intestinal illness lasting for less than twelve hours, and five to seven days later developed paratyphoid fever.

Five of the patients were holiday visitors and seven were from neighbouring areas, but 13 of them had eaten cakes filled with imitation cream (chocolate éclairs, cream buns, cream sponge) made in one bakery in Worthing between July 23 and August 6. Information was unobtainable from one person. No other common factor was found.

Bacteriological and serological examinations of the staff of the bakery and of the retail shops in which the cakes were sold were negative except for one woman who sold cakes in a retail shop and who had a gastro-intestinal illness on July 31, twelve hours after eating imitation-cream cakes. On August 25 she showed serological evidence of recent infection with *Salm. paratyphi B* although no salmonellae were found in her faeces or urine. She worked only in the retail shop and never in the bakery.

*Salm. paratyphi B* was not found in any home contacts of the patients, but one home contact was found to be excreting *Salm. thompson*.

Eight of the 13 patients whose food history is known ate cakes from retail shops outside Worthing but supplied by the central bakery. In these shops the time interval between production and consumption was some hours longer than with cakes sold in Worthing itself.

### Weymouth Outbreak

Fourteen visitors and residents in South Dorset had an enteric illness starting between August 18 and September 14, and were found to be excreting *Salm. paratyphi B* phage type 3a. The mother of two of the patients was found to be a symptomless excreter of the same phage type. Three persons were also excreting *Salm. thompson*. Two had a gastro-intestinal illness five to eleven days before the beginning of their enteric fever.

All those persons had eaten cakes from a baker in Weymouth seven to fourteen days before the onset of their enteric illness, and many of them regularly ate a wide variety of cakes from this source. Two main varieties of cake were made—sponge filled with "butter cream," and chocolate éclairs and cream buns filled with a proprietary imitation cream. While many of the patients had eaten cakes of both types, all of them had eaten cakes filled with the proprietary imitation cream.

Many of the patients had bought cakes from a van which called three times a week, and here, as in the Worthing outbreak, there was a longer interval between production and consumption than in purchases made from retail shops in the town.

Two members of the staff of the bakery were found to be excreting *Salm. paratyphi B* phage type 3a. One was a bookkeeper who ate cakes regularly and had an illness of the enteric fever type on August 28 and was found to be also excreting *Salm. thompson*. The other was an apprentice pastrycook who said that he had not been well since August 16 ; he had made no specific complaints, but had stopped work and visited his doctor on August 30. An assistant in the shop attached to this bakery was found to be a symptomless excreter of *Salm. thompson*.

Between August 18 and September 27 there were four other cases of enteric fever among residents or visitors to South Dorset. Two were found to be excreting *Salm. paratyphi B* phage type 3b, and two phage type Taunton. One of the patients excreting phage type 3b had eaten cakes from another bakery that had used Chinese frozen whole egg of the same consignment but was in no way connected with the original cases. There is insufficient evidence to associate these patients with those excreting *Salm. paratyphi B* phage type 3a.

### Products Used in Weymouth and Worthing Bakeries

The sources of those products thought to be relevant and used in the two bakeries at the suspected dates of infection were compared. They included frozen and dried whole egg, albumen, albumen products including marshmallow powders, flour, proprietary imitation creams, chocolate, sugar, essences, fillings, fondant, coconut, and fats. Many of these products were sampled separately and cakes filled with imitation cream were sampled in the course of manufacture.

The only product found in common was Chinese frozen whole egg packed in 22-lb. (10-kg.) upright cans, in single cartons, which had been imported by the Ministry of Food in the s.s. *Glenroy* in 1954.

The Worthing bakery accepted deliveries of this egg from July 14 to July 28 ; the batch was all used by July 31, when it was replaced by Turkish whole egg. No unopened cans of this shipment remained in Worthing when investigations were taking place, but one opened can which had been rejected by a baker because of its smell was sampled and found to contain *Salm. paratyphi B* phage type Taunton.

The Weymouth bakery used Chinese frozen whole egg in 44-lb. (20-kg.) cans until August 7, and then 22-lb. (10-kg.) cans ex s.s. *Glenroy*. This was in use until September 27, when a "standstill" order was placed on the remainder of this consignment in Weymouth under Section 18 of the Food and Drugs Act, 1938. On October 24 these cans were seized and destroyed by a Magistrate's Order under Section 10 of the Food and Drugs Act.

### Bacteriological Findings

Cakes in the course of manufacture and their constituents were examined by the Brighton and Dorchester Public Health Laboratories. *Salm. thompson* was found in an opened package of an albumen compound used for meringues in Weymouth; all other examinations were negative for salmonellae.

Between September 23 and October 6 samples from 152 22-lb. (10-kg.) cans of Chinese frozen whole egg ex s.s. *Glenroy* were obtained from the cold store which supplied the Weymouth bakery. The tops of the frozen cans were cleaned and burned with methylated spirit, and a 60–80-g. sample was bored out with a brace and sterile bit. These samples were examined by the Food Hygiene Laboratory at Colindale; the results from the Weymouth and Worthing samples are shown in Table I. The samples

TABLE I.—*Results of Examination for Salmonellae of Samples from* 153 22-*lb.* (10-*kg.*) *Cans of Chinese Frozen Whole Egg ex* s.s. "*Glenroy*"

| Salmonella | No. of Cans Contaminated |
|---|---|
| *Salm. thompson* .. .. .. .. .. | 20 |
| ,, *aberdeen* .. .. .. .. .. | 1 |
| ,, *pullorum* .. .. .. .. .. | 23 |
| ,, *paratyphi B* phage type Taunton .. | 2 |
| ,, ,, ,, ,, ,, 1 .. .. | 2 |
| ,, ,, ,, ,, ,, 3a .. .. | 2 |

TABLE II.—*Growth of Bacterium coli at* 22° *C. in Imitation Cream Alone and in Contact with Confectionery* (*Bun and Eclair*)

| Time | Surface Colony Count per Gramme | | |
|---|---|---|---|
| | Control (Alone) | Test on Bun | Test on Éclair |
| 0 hour .. .. | 60,000 | 70,000 | 75,000 |
| 1 day .. .. | < 500 | 3 million | 17,500 |
| 2 days .. .. | < 500 | 25 ,, | 100 million |
| 3 ,, .. .. | < 500 | 450 ,, | Not done |

were kept frozen until they were examined. Twenty-five-gramme quantities of egg were mixed with an equal amount of quarter-strength Ringer's solution and incubated at 37° C. for one to two hours, after which the appropriate amounts of double-strength selenite and tetrathionate liquid media were added; subcultures were made on deoxycholate citrate and Wilson and Blair agars after one day, and again after three days, for the selenite cultures (Smith and Hobbs, 1955).

Some cans contained more than one type of salmonella, and the two cans containing *Salm. paratyphi B* phage type 3a also contained *Salm. thompson* and *Salm. pullorum*.

Attempts were made to estimate the number of salmonellae present in samples from four cans containing *Salm. paratyphi B* and *Salm. pullorum*, two of which also contained *Salm. thompson*, by means of a technique similar to that used for the presumptive coliform count in water examination (Ministry of Health, 1939). The selenite fluid medium was used in place of MacConkey broth. The presumptive counts for *Salm. paratyphi B* varied from 10 to 1,800+ per 100 ml. The estimations were repeated and the counts of paratyphoid bacilli from one particular can were 250 and 1,800+ per 100 ml. on different occasions. From these results and from those given in Table I, it is clear that the organisms were distributed very irregularly, not only in different cans but in different parts of the same can.

*Salm. thompson* counts varied from 17 to 45 per 100 ml. The counts of *Salm. pullorum* were 1,800+ per 100 ml. in three cans and 600 per 100 ml. in one can.

Phage-typing of the paratyphoid B bacillus was introduced by Felix and Callow (1943) (see also Felix and Callow, 1951). The phage type of a strain of *Salm. paratyphi B* is for all practical purposes a stable characteristic, and its identification provides a "finger-print" whereby groups of cases of paratyphoid fever may be defined and linked up with their source of infection. It has been used in this way in these two outbreaks and also for tracing an organism from a contaminated vehicle through the bakery to the patients. The phage-typing in this investigation was carried out by the Central Enteric Reference Laboratory and Bureau, Colindale. Because no similar procedure was available for *Salm. thompson*, it was not possible to discover whether the bakery staff and the patients excreting this organism were infected through frozen whole egg or through albumen.

### Discussion

Two outbreaks of paratyphoid fever associated with imitation-cream cakes made in commercial bakeries have been investigated. The connexion with the bakery was strengthened in the Weymouth outbreak by the finding of the same phage type of paratyphoid B bacillus in two members of the staff. The vague illness of the apprentice pastrycook occurred seven days after the first use of a contaminated batch of Chinese frozen whole egg, and four days before the onset of illness of the first patient. Even if this boy was indirectly responsible for some of the early cases, the fact that the onset of illness of the last Weymouth patient was 27 days after the boy had stopped working shows that he is unlikely to have been responsible for all of them.

Three questions require consideration.

(*a*) Why is it, if the Chinese egg was the original source of infection, that the cases were caused only by *Salm. paratyphi B* phage type 3a? It is impossible to answer this question satisfactorily. Examination, however, of Table I, taken in conjunction with the results of examining large numbers of other batches of Chinese frozen whole egg, leaves no doubt that this product is extensively contaminated with different members of the *Salmonella* group, including *Salm. paratyphi B*. The product in any one can is not homogeneous, and the organisms are therefore not distributed uniformly throughout the mass. It follows that which particular organism gains access to a given batch of cakes filled with imitation cream must be largely a matter of chance. Though these particular outbreaks were caused by *Salm. paratyphi B* phage type 3a, it may be noted that in Weymouth there were other cases, having a possible association with the bakery, which were infected with phage type Taunton—one of the three phage types of paratyphoid bacilli found in the frozen whole egg.

The evidence incriminating the egg is strengthened by the findings that in the Worthing outbreak two patients and one healthy person were excreting *Salm. thompson*, and in the Weymouth outbreak three of the patients and two members of the bakery staff were excreting this organism. Apart from *Salm. pullorum*, which is usually non-pathogenic to man, *Salm. thompson* is found more often than any other type of salmonella in Chinese frozen egg. This organism is the third commonest type of salmonella in food-poisoning in this country, and is seldom found in any other article of food than egg. The occurrence of eight cases of *Salm. thompson* infection in the Worthing and Weymouth outbreaks associated with a batch of frozen egg that contained large numbers of this particular type of organism cannot but be regarded as aetiologically significant.

(*b*) If Chinese frozen egg was the original source of infection, how did it lead to contamination of the imitation-cream cakes? Interrogation of the master pastrycooks in the two bakeries concerned revealed that the cans of egg had been stored in the same refrigerator as the cans of imitation cream, and that the same dispensing measures

had been used for both products. Though egg was not represented in the formula of the imitation cream, it nevertheless often gained access to the cream fortuitously.

(*c*) If paratyphoid bacilli gained access to the imitation cream, would the cream be thereby rendered infective for man? There is reason to believe that paratyphoid bacilli are able to give rise to disease in man only when ingested in considerable numbers. It may therefore be assumed that multiplication of the organism must occur in the cream before this becomes infective. Hobbs and Smith (1954) showed that synthetic cream could be divided into two groups—those that supported bacterial growth and those that did not. They further showed, in confirmation of Thomson's (1953) work, that cream belonging to the second group was converted into a rich nutrient medium by contact with flour, cakes, or other source of protein. This is illustrated by Table II, kindly provided by Miss J. Glanville, which shows that *Bact. coli*, though actually dying in imitation cream itself, multiplied abundantly when the cream was kept at room temperature in contact with buns or éclair casings.

The length of time required for sufficient growth of paratyphoid bacilli to occur to render the cakes infective must necessarily depend upon many factors, such as the number of paratyphoid bacilli introduced initially, the number of other organisms present, the nature of the cake or other mixture into which the cream is brought into contact, the degree of heating, if any, that the cake may receive, and the time and temperature of incubation in the shop, on the round, and in the customer's home. In this connexion it is interesting to notice that most of the patients in these two outbreaks had bought their cakes, not directly from the bakery where they were made, but from outlying shops supplied by the bakery or from a roundsman. Under these conditions there was almost certainly a delay in the consumption of the cakes, thus favouring the multiplication of the organism in the cream.

We have assumed here that the cream acted as the direct vehicle of infection. It must be realized, however, that, once contamination is introduced into a bakery, other articles must inevitably become contaminated. Many of these articles will be epidemiologically of no importance, because they will be subjected in baking to a sufficient degree of heat to kill off non-sporing pathogenic organisms such as those of the *Salmonella* group. It is because imitation cream is not subjected to any serious heat treatment after it has been added to articles of confectionery, and because, in conjunction with nutrient materials provided by the cake itself, it provides such an excellent pabulum for bacterial growth, that it must be regarded as of special potential danger.

To protect against outbreaks of this sort known contaminated products must be prevented from gaining access to a bakery. Hobbs and Smith (1954) suggested the use of hydrogen peroxide to prevent the growth of any pathogenic organisms that may gain access to synthetic cream adventitiously.

It need hardly be added that strict control should be kept over the health of employees in bakeries; but the experience of the Public Health Laboratory Service has shown that, though cases and symptomless excreters are not uncommon among bakery employees, they almost invariably give a history of having eaten the contaminated cream buns or cakes. There is growing evidence to support the view that bakery products usually become contaminated not primarily from infected members of the staff but from inanimate articles introduced from outside, of which Chinese processed egg in its various forms is the most common.


### Summary

Two outbreaks of paratyphoid fever due to *Salm. paratyphi B* phage type 3a are described.

The vehicle of infection was cakes filled with a proprietary imitation cream used in two bakeries.

The same phage type of paratyphoid bacillus was found in unopened cans of Chinese frozen whole egg used in the bakeries, in some members of the staff, and in the patients.

It is suggested that the imitation cream was contaminated within the bakery by *Salm. paratyphi B* from the frozen whole egg.

The dangers of the use of a contaminated product in a bakery are discussed.


We are grateful to Dr. E. S. Anderson and the staff of the Central Enteric Reference Laboratory and Bureau for phage-typing; to the Dorchester and Brighton Public Health Laboratories for the results of the examinations of specimens from cases and the bakeries; to Miss Muriel E. Smith and the staff of the Food Hygiene Laboratory, Colindale, who examined the egg samples; and to Mr. F. Marsh and his staff for the preparation of large quantities of media. We would especially like to thank Dr. G. H. Pringle, Medical Officer of Health of the Borough of Worthing, and Dr. F. Cockcroft, Medical Officer of Health of Worthing Rural District, and their staffs, for permission to publish this account of their outbreak and for assistance with sampling. We also thank the medical officers of health of several other areas for information about patients in their areas.

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## JAMSHEDPUR FEVER*


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Jamshedpur fever is the name given to a peculiar illness which started in the city of that name and affected children and young adults, having the highest mortality among the very young. Later it spread to other cities such as Lucknow, Delhi, Kanpur, Allahabad, Calcutta, and Nagpur. Jamshedpur, unlike some of its neighbours, is a clean and well-planned city with a population of about 251,619 (1951 census); it has a very fine water supply and an excellent sewage system. The standard of health among the population, which consists largely of employees in the iron and steel industry and their families, is good.

The illness was first observed in Jamshedpur on May 14, 1954. A child about 1 year of age suddenly developed respiratory distress with a temperature of 103° F. (39.4° C.). Moist sounds were heard on both sides of the chest, and a provisional diagnosis of broncho-pneumonia was made. The child died in two hours. About a fortnight later another child from the same

*Abridged from a paper read at the symposium on "The Mystery Disease in India" held during the All India Annual Conference of Physicians, 1955, at Nagpur.

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house and family became ill with a temperature of 102° F. (38.9° C.). There were no areas of consolidation in the chest, but a few crepitations were heard on auscultation. The child did not appear very ill or toxic. Since the first patient had been treated with tetracycline without success this child was given injections of procaine and crystalline penicillin, 210,000 units of each, the latter to be repeated every three hours. In spite of this the child died within a few hours. The occurrence of two fatal cases of a similar type in the same house within such a short time raised the possibility of an infectious disease, which later seemed to be confirmed when similar cases occurred of children who died a few hours after a sudden rise of temperature.

It was decided that this was a disease hitherto not met with in Jamshedpur. The clinical pattern was the same in all the fatal cases. Cerebral malaria, which is common in Jamshedpur, was ruled out, as malaria parasites were not found on repeated examination in any of the cases. The enteric group of fevers, typhus, brucellosis, and leptospiral infections were all excluded both bacteriologically and serologically. The exclusion of protozoal and bacterial causes pointed to the possibility of a virus infection, probably a virus encephalitis. A team of experts headed by Dr. Telford H. Work, Assistant Director of the Virus Research Centre, Poona, and Dr. T. Ramachandra Rao, medical entomologist, were sent to investigate the outbreak.

## Fatal Cases

From May to September, 1954, 35 fatal cases were admitted to the Tata Main Hospital, Jamshedpur. In Fig. 1 the total number of deaths in the hospital and the deaths among children in the years 1952, 1953, and 1954 are compared. The total number of deaths among children during May to September in the years 1953 and 1954 and the fatal cases of Jamshedpur fever are given in Table I.

Thus for the period May to September, 1954, out of a total of 93 deaths among children, 35, or 38%, were due to Jamshedpur fever, the maximum fatality (17 out of 19) occurring in June. Although the number of fatal cases is small when compared with the total number of deaths in the hospital, the fact that it refers to only one disease makes it significant.

TABLE I.—*Total Deaths Among Children Compared with Deaths from Jamshedpur Fever*

| | May | June | July | Aug. | Sept. | Total |
|---|---|---|---|---|---|---|
| 1953.. .. | 12 | 19 | 2 | 21 | 15 | 79 |
| 1954.. .. | 12 | 19 | 26 | 19 | 17 | 93 |
| Jamshedpur fever | 2 | 17 | 8 | 5 | 3 | 35 |

### Age Incidence and Distribution

The ages ranged from 1 to 26 years, although most of the patients were in the younger age groups. The incidence according to age group in the 35 cases was as follows: 1–5 years, 12 (8 males); 6–10 years, 19 (12 males); 11–15 years, 2 (males); over 15 years, 2 (males). Thus it can be seen that most of the fatal cases occurred between the ages of 1 and 10, and that males predominated.

The distribution of the cases is shown on the map of Jamshedpur (Fig. 2), from which it can be seen that they came from all parts of the city.

### Clinical Features

The usual history was that the child was well and playing during the day, but that during the night there was a sudden rise of temperature, or an attack of convulsions, or the child muttered deliriously in his sleep. Within two or three hours the temperature reached 104° or 105° F. (40° or 40.6° C.), and in a few cases even 106° F. (41.1° C.). Excessive thirst was common.

When seen, these children were obviously toxic and ill. Some had convulsions, and a few had twitching of muscles and clenching of teeth. Even when patients were conscious on admission, coma or a muttering delirium set in as the temperature rose. The disease ran such a rapid course that many patients died within an hour or two of their admission before any investigation was possible. Patients were flushed and irritable. The skin was dry and hot, and the tongue coated and dry. Neck rigidity was present in a few cases, but was not a constant feature. Pupils were irregular, dilated, and reacted sluggishly to light. Photophobia was not noted. Superficial and deep reflexes, even if brisk at the time of admission, usually could not be elicited as the condition deteriorated. The plantar response was extensor and abdominal reflexes were absent. The pulse rate was slow in relation to the raised temperature. Fundi were congested, with no haemorrhagic areas. In a few cases one or

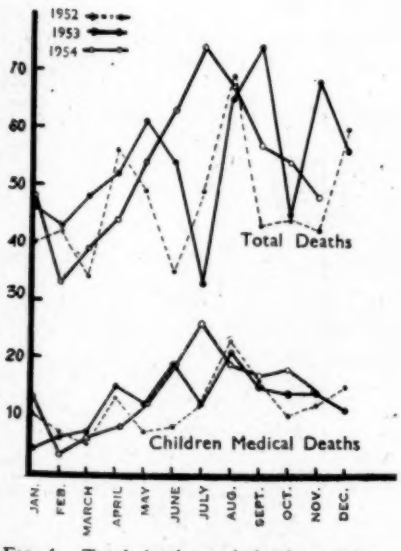


FIG. 1.—Total deaths and deaths among children, 1952–4.

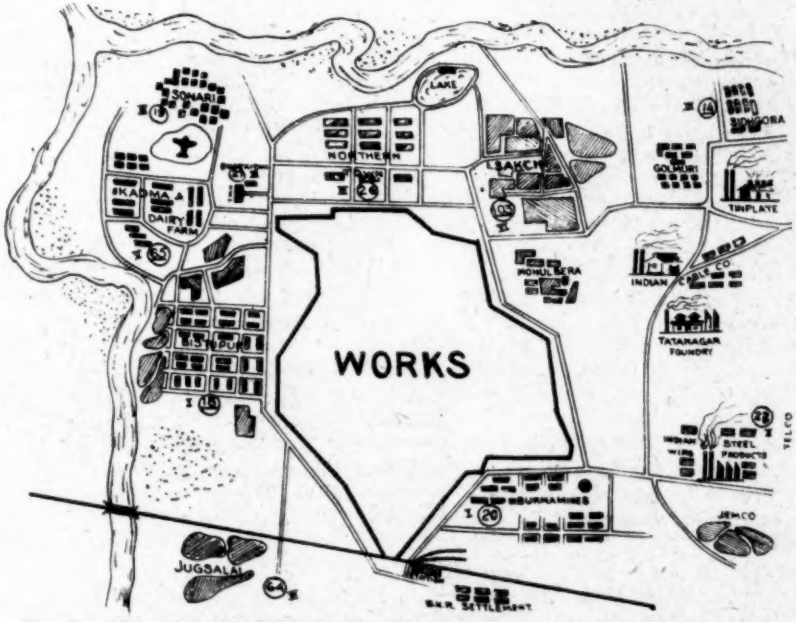


FIG. 2.—Map of Jamshedpur showing distribution of cases (fatalities in roman numerals).

two loose motions were passed after admission. Respiratory, cardiovascular, and other systems were all normal. There was no enlargement of liver or spleen. Towards the end bubbling rales developed on both sides of the chest and became progressively worse. No improvement followed the administration of oxygen, nor did artificial respiration have any effect in prolonging life. All the children died within 24 hours of the onset of the illness.

### Laboratory Investigations

As stated earlier, bacteriological and serological tests gave negative results in all cases. Leucocytosis with increase in polymorphs, seen in a few cases, was not a constant feature. Lumbar puncture was performed in 21 of the 35 fatal cases. Results of the cerebrospinal fluid (C.S.F.) examination are given in Table II.

TABLE II.—*Results of C.S.F. Examination* (21 *Cases*)

| Amount in mg. per 100 ml. | No. of Cases | Amount in mg. per 100 ml. | No. of Cases |
|---|---|---|---|
| **SUGAR** | | | |
| Below 20 | 2 | 51–60 | 2 |
| 21–30 | 1 | 61–70 | 6 |
| 31–40 | 2 | 71–80 | 2 |
| 41–50 | 1 | 81–90 | 5 |
| **PROTEIN** | | | |
| Below 20 | 8 | 41–50 | 1 |
| 21–30 | 10 | Above 100 | 1 |
| 31–40 | 1 | | |
| **CHLORIDES** | | | |
| 601–700 | 7 | 701–800 | 14 |

The globulin fraction was increased only in the case with a protein level above 100 mg. Lymphocytes were present and there was no pleocytosis. Blood sugar was estimated in 13 of the cases. In only three of the nine cases in which blood and C.S.F. sugar was estimated was there a fall in both levels (see Table III).

TABLE III.—*C.S.F. and Blood Sugar Values in* 3 *of* 9 *Cases Examined*

| C.S.F. Sugar (mg. per 100 ml.) | Blood Sugar (mg. per 100 ml.) |
|---|---|
| 55·5 | 20 |
| 35·35 | 40 |
| 31·2 | 44·4 |

Blood sugar values in the 13 cases are given in Table IV.

TABLE IV.—*Analysis of Blood Sugar Readings* (13 *Cases*)

| Amount in mg. per 100 ml. | No. of Cases | Amount in mg. per 100 ml. | No. of Cases |
|---|---|---|---|
| Below 20 | 3 | 61–70 | – |
| 21–30 | — | 71–80 | 1 |
| 31–40 | 1 | 81–120 | 3 |
| 41–50 | 1 | Above 120 | 3 |
| 51–60 | 1 | | |

In one case the blood sugar level was 44.4 mg. per 100 ml. at the time of admission, rose to 112 mg. after glucose administration, fell to 18.2 mg. after three hours, and rose again to 61 mg. just before the patient's death. In another case blood sugar was 28.5 mg. and C.S.F. sugar 32.1 mg. per 100 ml., the blood sugar reaching 284.8 mg. per 100 ml. after glucose administration. In this case, diagnosed soon after admission as Jamshedpur fever, blood and C.S.F. sugar estimations were made every four hours; no appreciable fall in blood sugar level was noticed after the glucose administration.

It is apparent that the C.S.F. and blood sugar levels tended to fall in some of the fatal cases. There was no abnormal increase in C.S.F. proteins, however, in any of the cases except one. Intravenous and oral administration of glucose did not affect the prognosis in any way, as all the children so treated died. After glucose had been given the blood sugar level rose and sugar was detected in the urine.

In the three cases in which blood urea and calcium were estimated these were normal. In one case a chest radiograph was normal.

### Treatment

Injections of procaine and crystalline penicillin, oxytetracycline, chloramphenicol, chlortetracycline, and tetracycline were tried in different cases, but none of these antibiotics was found to be effective.

### Post-mortem Examination

Necropsy was possible in only one case, because of the popular objection to such examinations. Sections of various organs—brain, liver, spleen, kidneys, heart, suprarenals—were collected by Dr. Work. No changes were noticeable in these organs on either macroscopical or microscopical examination. There was no glycogen depletion in the liver. Further investigations on a possible viral aetiology of the disease are being carried out at the Virus Research Centre, Poona.

## Non-fatal Cases

Parallel with the increase in the number of fatal cases there was a sudden increase in the number of admissions to the medical wing of the hospital. Fig. 3 shows graphically

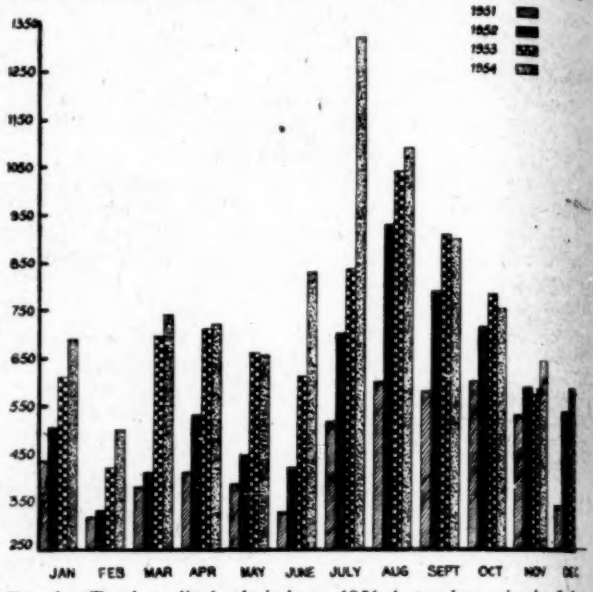


FIG. 3.—Total medical admissions, 1951–4, to show rise in July, 1954, as compared with other years.

the total admissions to the medical wards for the years 1951–4, the rise in July, 1954, being striking. Admissions to the children's medical ward for the years 1953 and 1954 are compared in Fig. 4. The increase in 1954 was due to the admission of a number of cases with a rise of temperature which was sudden in onset, lasted for a day, and then subsided either by crisis or by lysis within 24 to 48 hours. A total of 378 such cases were admitted to one department of the hospital during the period in question. These cases, like the fatal cases, were all bacteriologically and serologically negative. Since the deaths in very young children and these non-fatal cases occurred coincidently it was concluded that both belonged to the same group, the disease being fatal or severe in the very young and mild in the older age group.

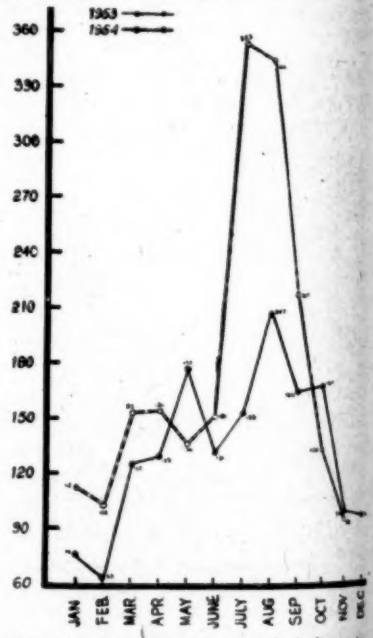


FIG. 4.—Comparison of admissions to children's medical ward in 1953 and 1954.

TABLE V.—*Classification According to Age and to Type of Infection of 378 Non-fatal Cases (Figures in parentheses denote Females)*

| Age Group (Years) | May | | | June | | | July | | | August | | | September | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total Admitted | Severe | Mild | Total Admitted | Severe | Mild | Total Admitted | Severe | Mild | Total Admitted | Severe | Mild | Total Admitted | Severe | Mild | Admissions | Severe | Mild |
| Under 1 | 0 | 0 | 0 | 6 | 1 | 5 | 14 (8) | 3 (2) | 11 (6) | 14 (5) | 0 | 14 (5) | 4 (2) | 0 | 4 (2) | 38 (15) | 4 (2) | 34 (13) |
| 1–10 | 1 (1) | 1 (1) | 0 | 22 (6) | 10 (2) | 12 (4) | 67 (25) | 14 (6) | 53 (19) | 32 (12) | 1 | 21 (12) | 5 (3) | 0 | 5 (3) | 127 (47) | 26 (9) | 101 (38) |
| 11–20 | 2 | 0 | 2 | 27 (9) | 4 (2) | 23 (7) | 29 (9) | 1 | 28 (9) | 11 (5) | 0 | 11 (5) | 5 (2) | 0 | 5 (2) | 74 (25) | 5 (2) | 69 (23) |
| 21–30 | 3 (1) | 0 | 3 (1) | 30 (6) | 0 | 30 (6) | 21 (12) | 0 | 21 (12) | 8 (3) | 0 | 8 (3) | 1 | 0 | 1 | 73 (22) | 0 | 73 (22) |
| 31–40 | 5 (2) | 0 | 5 (2) | 19 (3) | 0 | 19 (3) | 22 (4) | 0 | 22 (4) | 8 (3) | 0 | 8 (3) | 2 | 0 | 2 | 56 (12) | 0 | 56 (12) |
| 41–50 | 0 | 0 | 0 | 3 (1) | 0 | 3 (1) | 4 (1) | 0 | 4 (1) | 0 | 0 | 0 | 0 | 0 | 0 | 7 (2) | 0 | 7 (2) |
| Over 50 | 1 | 0 | 1 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 |
| Total | 12 (4) | 1 (1) | 11 (3) | 109 (25) | 15 (4) | 94 (21) | 167 (59) | 18 (8) | 149 (51) | 73 (28) | 1 | 72 (28) | 17 (7) | 0 | 17 (7) | 378 (123) | 35 (13) | 343 (110) |

### Clinical Features

The non-fatal cases may be divided into two broad groups—with (1) severe and (2) mild infection. The first group (severe type) was mostly composed of children and young adults. There was a sudden rise of temperature to 103° F. (39.4° C.), with or without rigors, accompanied by severe muscular pain in the limbs and backache, almost dengue-like in nature. Congestion of the eyes and a dry, coated tongue were features. The patient was usually drowsy and apathetic, lying curled on one side and irritable if disturbed. Bradycardia was another feature. Neck rigidity, Kernig's sign, and pupillary changes were present only in the very severe cases. Ankle and knee jerks were brisk and plantar responses extensor. The temperature subsided either suddenly or gradually in the course of two or three days, depending upon the severity of the illness. Respiratory, cardiovascular, and other systems were normal.

Patients in the second group (mild type) had a sudden rise of temperature, with muscular pains. The fever lasted only 24 hours or at most two days, after which recovery set in.

In a few cases in both groups the temperature rose again about three or four days after the onset.

The age distribution and classification according to type of disease in the 378 non-fatal cases are given in Table V.

### Incubation Period

The incubation period varied from two to seven days. A child visiting Jamshedpur for the first time developed a fatal illness after a week's stay. Another child contracted the fever two days after arriving in the city. Four days after his arrival from Madras the son of one of us (M. V. C.), aged 4 years, developed a sudden rise of temperature during the night. He complained of excessive thirst, woke up with a start every two or three hours throughout the night feeling frightened and with symptoms of mental irritability. The clinical picture conformed to that in the severe, non-fatal type described, and the patient recovered within 24 hours.

### Laboratory Investigations

As already stated, both bacterial and protozoal causes for the infection were excluded. An analysis of the total leucocyte counts is given in Table VI. In a number of cases the urine contained a trace of albumin, probably due to the fever. In some of the cases a few pus cells were also present. On cultural examination urine was sterile and no pathogens were isolated from the faeces.

Blood sugar, blood urea, and serum calcium levels and van den Bergh reaction were all normal. As in the fatal cases, examination of the C.S.F. gave normal results, the protein level remaining constant at about 15 mg. per 100 ml.

TABLE VI.—*Total Leucocyte Counts*

| | Leucocyte Count (per c.mm.) | | | | Total Cases |
|---|---|---|---|---|---|
| | 5,000–10,000 | 10,001–15,000 | 15,001–20,000 | Above 20,000 | |
| No. of cases .. | 229 | 92 | 39 | 18 | 378 |

### Relapses

After their discharge a number of patients returned to the hospital in a week to ten days with another attack of a similar nature. These cases are analysed in Table VII.

TABLE VII.—*Relapses (Females in Parentheses)*

| All Groups (Years) | May | June | July | Aug. | Sept. | Total |
|---|---|---|---|---|---|---|
| Under 1 .. | — | 2 | — | 1 | — | 3 |
| 1–10 .. | — | 8 (1) | 16 (5) | 3 (2) | — | 27 (8) |
| 11–20 .. | — | 10 (5) | 1 | 4 (1) | — | 15 (6) |
| 21–30 .. | — | 1 | 2 | — | — | 3 |
| 31–40 .. | — | 3 | 2 | 1 | — | 6 |
| Total .. | — | 24 (6) | 21 (5) | 9 (3) | — | 54 (14) |

### Treatment

In the non-fatal, as in the fatal, cases no antibiotic was effective. Antipyretics together with symptomatic treatment to control the pains in the limbs and headache were given.

### Neurological and Mental Manifestations

Only two children developed paresis of an upper motor neurone type, one during the course of the illness and the other while convalescent. The former had paralysis of the arms and legs, and he did not recover the use of his limbs till one month after discharge. The other patient had paralysis of the left arm, which developed four days after the fever had subsided. He started to regain the use of the arm 12 days after the onset of the paresis and is now completely cured. Two patients, a girl aged 8 and a boy aged 5, showed mental changes. Both were normal and healthy before the illness, which was severe. The girl had symptoms of mental instability during a relapse, and the boy showed mental changes when his temperature returned to normal.

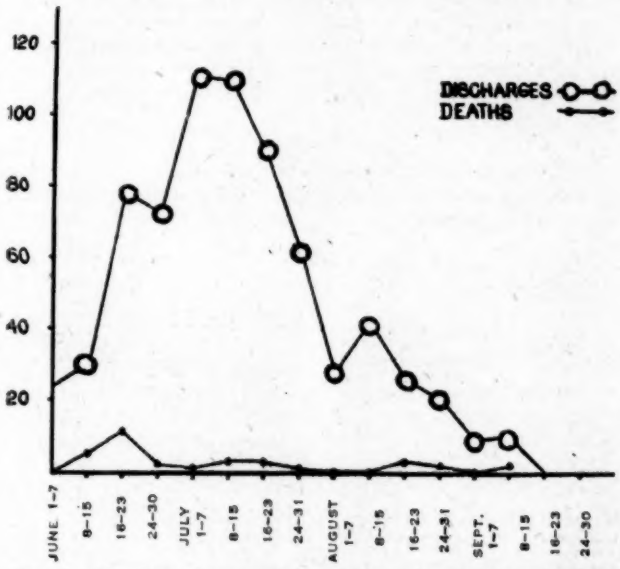


FIG. 5.—Number of cases of Jamshedpur fever discharged each week and number of fatal cases.

Both had completely recovered when discharged ten days later. No reports of the development of paralysis or mental changes in any cases subsequent to discharge from hospital have so far been received.

### Relationship Between Fatal and Non-fatal Cases

It was presumed that both the fatal and the non-fatal cases had the same aetiology because they appeared at the same time. Fig. 5 shows the number of cases of Jamshedpur fever discharged each week, and the number of fatal cases. It will be noted that, while the maximum incidence of fatal cases was in June, the number of non-fatal cases increased in July. One of the reasons for this might be the development of a certain degree of immunity.

### Increased Incidence of Anterior Poliomyelitis

Anterior poliomyelitis is not common in Jamshedpur, only one acute case being seen in 1953 at this hospital. In 1954, however, the number of cases of poliomyelitis had increased (see Table VIII), and there were two deaths in the hospital. Virus was isolated from one of these fatal cases.

TABLE VIII.—*Cases of Anterior Poliomyelitis Occurring Simultaneously with the Outbreak of Jamshedpur Fever*

| | June | July | Aug. | Sept. | Oct. | Nov. | Total |
|---|---|---|---|---|---|---|---|
| No. of cases .. | 0 | 2 | 4 | 2 | 1 | 1 | 10 |

Except for two cases in children aged 3 and 5 years, all the patients were below 2 years of age.

Any relationship between Jamshedpur fever and anterior poliomyelitis has not been established, and it is presumed that they are not interrelated, the appearance of both diseases about the same time being probably a coincidence.

### Epidemiological Aspects

#### Climatic Factors

Jamshedpur is at an altitude of 550 feet (168 metres) above sea level. The average monthly rainfall, maximum and minimum temperatures, and humidity for the years 1952–4 are given in Table IX.

It can be seen that in 1954 there was a diminished rainfall in Jamshedpur for the months of June, July, and August as compared with the previous two years. Whether this is a likely cause in the spread of this disease is difficult to say.

#### Locality and Economic Factors

On analysing the cases according to locality it was found that the disease was not confined to one region or to one section of the population. The map of Jamshedpur (Fig. 2) shows the distribution of the fatal and non-fatal cases. Children from both the poor and the better-off classes were affected.

#### Arthropods

Although the fatal, severe, and mild cases were all treated in the same ward as other children, and although surgical cases were housed in another wing of the same building with a common dining-hall, cross-infection inside the hospital was unlikely. It was only very rarely that more than one case occurred in the same family. Direct spread of the disease was therefore ruled out. In view of this, the possibility of an arthropod vector was considered. Dr. T. Ramachandra Rao, of the Virus Research Centre, Poona, worked along these lines for nearly four months, and his findings are summarized below.

The blood-sucking arthropods found in houses during the daytime were almost entirely mosquitoes (*Anopheles, Aëdes,* and *Culex*) and sandflies (*Phlebotomus papatasii* and *P. minutus*). Houseflies were present in moderate numbers in all the houses. On the assumption that one of these arthropods might be responsible for transmitting the disease it was decided to start anti-arthropod measures. To assess the results of these measures three contiguous areas—Kadma, Sakchi, and Northern Town—approximately 4 miles (6.5 km.) long and 1 mile (1.6 km.) wide were chosen. The number of houses in this area was about 11,515 with a population of 96,559 (1951 census). "Gammexane P 520," a 50% water-wettable powder of benzene hexachloride, was used for spraying the interior of all houses and cattle-sheds in the selected area, 16,473 lb. (7,470 kg.) of gammexane being used. Gammexane was chosen in preference to D.D.T. because of its higher initial toxicity effective over a wider range of arthropods. The spraying extended from July 1 to 30, and served 38.4% of the population.

This resulted in the immediate disappearance of both mosquitoes and sandflies, while their number remained unaffected in the unsprayed sectors. By September–October in the unsprayed sectors the density of mosquitoes had reached 14.9 per man-hour of search, and that of sandflies 7.8; whereas the corresponding figures in the sprayed sectors were 3.4 and less than 0.04. Houseflies also disappeared for a few weeks from the sprayed houses, reappearing in small numbers towards the end of September.

TABLE X.—*Distribution of* 893 *Cases of Jamshedpur Fever*

| | Sprayed Sectors | Unsprayed Sectors | Total |
|---|---|---|---|
| Population (1951) | 96,559 | 155,060 | 251,619 |
| No. of cases: | | | |
| Fatal .. .. | 15 | 20 | 35 |
| Severe .. .. | 32 | 30 | 62 |
| Mild .. .. | 421 | 375 | 796 |
| Total .. | 468 | 425 | 893 |
| Average per 1,000 population .. | 4·8 | 2·7 | 3·5 |

A total of 893 cases (including the 35 fatal cases) were analysed by Dr. Rao according to area of origin; his findings are given in Table X.

In Table XI the 893 cases are analysed with reference to their time of admission.

Fig. 6 shows graphically the distribution of severe and fatal cases in the sprayed and unsprayed areas and in the whole town; it also shows the number of cases admitted every four days.

TABLE IX

| Month | Temperature (°F.) Maximum | | | Temperature (°F.) Minimum | | | Humidity (%) | | | Rainfall (inches) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1952 | 1953 | 1954 | 1952 | 1953 | 1954 | 1952 | 1953 | 1954 | 1952 | 1953 | 1954 |
| January .. | 88·0 | 84·0 | 86·5 | 46·4 | 44·0 | 44·0 | 69 | 72 | 72 | Nil | 0·12 | 0·05 |
| February .. | 96·8 | 96·0 | 95·3 | 54·2 | 48·8 | 54·7 | 58 | 65 | 60 | 0·30 | 0·05 | 0·36 |
| March .. | 103·0 | 107·0 | 105·0 | 58·0 | 64·4 | 53·7 | 54 | 47 | 39 | 0·40 | — | 0·02 |
| April .. | 107·8 | 109·6 | 111·2 | 69·8 | 66·3 | 68·0 | 57 | 38 | 37 | 2·90 | 0·20 | 0·03 |
| May .. | 109·0 | 114·0 | 112·0 | 72·0 | 73·0 | 76·1 | 63 | 55 | 54 | 1·75 | 1·30 | 1·03 |
| June .. | 112·0 | 113·6 | 101·0 | 73·8 | 71·8 | 74·8 | 70 | 72 | 71 | 9·75 | 7·50 | 5·25 |
| July .. .. | 97·4 | 94·2 | 98·0 | 74·7 | 74·4 | 76·0 | 84 | 83 | 79 | 19·80 | 16·60 | 5·00 |
| August .. | 93·0 | 92·7 | 95·1 | 78·9 | 73·7 | 77·0 | 82 | 83 | 82 | 9·80 | 19·80 | 8·24 |
| September | 93·5 | 93·0 | 93·6 | 78·0 | 74·4 | 74·2 | 80 | 81 | 82 | 5·50 | 7·70 | 7·25 |
| October .. | 93·0 | 94·0 | 93·0 | 72·3 | 58·3 | 59·0 | 72 | 76 | 73 | 2·80 | 0·20 | 1·69 |
| November | 89·7 | 86·4 | 87·0 | 48·0 | 53·8 | 52·6 | 71 | 75 | 68 | 0·10 | 3·65 | — |
| December .. | 86·0 | 82·3 | — | 58·5 | 53·0 | — | 76 | 79 | — | — | — | — |

TABLE XI.—*Analysis of 893 Cases According to Time of Admission*

| | Sprayed Sectors | | Unsprayed Sectors | | Total | |
|---|---|---|---|---|---|---|
| | No. of Cases | Rate per 1,000 Pop. | No. of Cases | Rate per 1,000 Pop. | No. of Cases | Rate per 1,000 Pop. |
| May 2–31 (30 days) | 21 | 0·22 | 26 | 0·17 | 47 | 0·19 |
| June 1–30 (30 days) | 137 | 1·42 | 116 | 0·75 | 253 | 1·01 |
| July 1–30 ( " ) | 205 | 2·12 | 192 | 1·24 | 397 | 1·58 |
| July 31–Aug. 29 (30 days) | 77 | 0·80 | 64 | 0·41 | 141 | 0·56 |
| Aug. 30–Sept. 18 (20 days) .. | 28 | 0·29 | 27 | 0·18 | 55 | 0·22 |
| Total .. | 468 | 4·80 | 425 | 2·70 | 893 | 3·50 |
| Estimated figures for Sept (30-day period) .. | 42 | 0·43 | 41 | 0·27 | 83 | 0·33 |

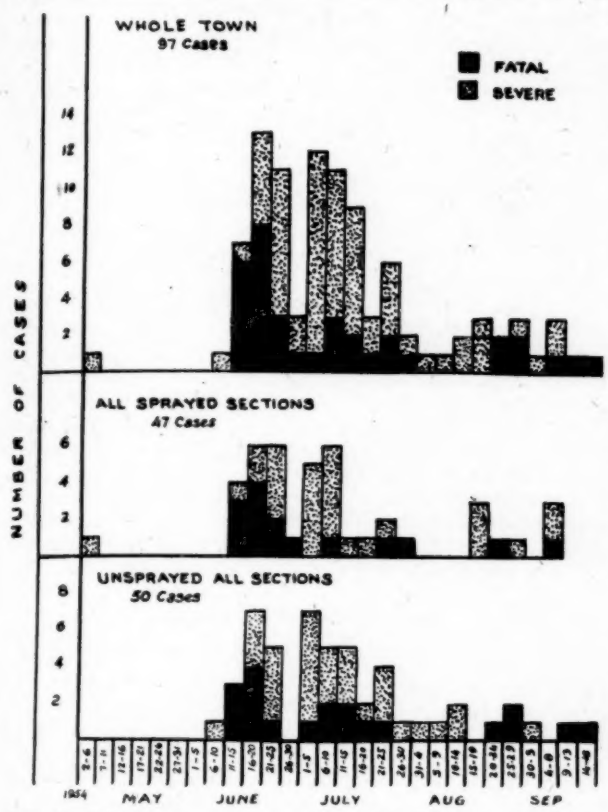


FIG. 6.—Distribution of severe and fatal cases in relation to spraying.

It will be noted that the application of 16,473 lb. (7,470 kg.) of gammexane inside 11,515 houses in a selected area had no effect on the incidence of Jamshedpur fever. The spraying was carried out at the peak of the epidemic, and the decline in incidence was essentially parallel in both the unsprayed and sprayed areas of the city.

### Preliminary Result of Serological Study at the Virus Research Centre, Poona

Although the gammexane spraying appeared to demonstrate that the infection was not arthropod-borne, neutralization tests on sera collected both from the acute cases of Jamshedpur fever and from the population at large indicated that there is a high degree of immunity to Type I dengue virus among the residents of Jamshedpur. There was also a substantial incidence of neutralizing antibodies to West Nile virus. The significance of these findings is yet to be determined.

A strain of Group A Coxsackie virus was isolated from the faeces of an 18-months-old child with a diagnosis of Jamshedpur fever. Serum from this patient, in which no antibodies to this virus were found during the acute phase, showed a high antibody content during the convalescent stage. But serological studies with acute and convalescent sera from other cases of Jamshedpur fever and "survey" sera from healthy children of 7–10 years showed a considerable amount of antibody to this strain of Coxsackie virus. These studies suggested that this agent was not responsible for the infection, although an intestinal route of spread is a possibility.

### Summary

The 35 fatal cases of an unidentified fever which occurred among children in Jamshedpur, Bihar, during the months of May to September, 1954, have been analysed. The cerebrospinal fluid had a normal protein content in most of the cases. Low C.S.F. sugar and low blood sugar levels were found in a few cases. Treatment with antibiotics had no effect in these cases.

In 378 non-fatal cases admitted to one medical department of a hospital the disease was severe or mild and occurred with or without relapses. Two children developed paresis and two showed mental changes during the illness.

The incidence of anterior poliomyelitis was found to have increased side by side with that of Jamshedpur fever.

The incubation period and epidemiological features are discussed.

Selected areas of the city were sprayed with gammexane to try the effect of anti-arthropod measures on the spread of the disease. This did not affect the incidence, the number of cases in the sprayed and unsprayed areas remaining unchanged.

Serological studies on the possibility that a virus was the aetiological agent are still being carried out at the Virus Research Centre, Poona; a preliminary report of the findings is given.

We thank Lieutenant-General K. S. Master, *M.C.*, I.M.S. (rtd.), Director of Medical and Health Departments, for giving us help and facilities in the preparation of this paper and permission to use the hospital records; also Dr. B. B. Dutta, junior pathologist, and Dr. J. Mahanty, assistant medical officer, for help with the clinical and laboratory investigations, and Dr. E. N. Murthy, R.M.O. Our thanks are also due to Dr. G. Singh for the illustrations. To Drs. Telford H. Work and T. Ramachandra Rao, who worked day and night in trying not only to arrest the spread of the disease but also to isolate the causal organism, we owe a great deal. Our sincere thanks are due to Dr. J. Austin Kerr, Director, Virus Research Centre, Poona, for guidance in the investigation and for permission to quote from Dr. Rao's report. We are grateful to both Drs. Kerr and Work for the sections dealing with the necropsy findings and the preliminary report of the serological study at the Virus Research Centre.

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Claims that the use of any toothpaste will cure or prevent dental decay are denied by the British Dental Association in a recent statement. The association favours tooth brushing to clean the teeth, but says that cleaning is all that a toothpaste can do. "The British Dental Association," the statement reads, "recognizes that a dentifrice is of considerable value in the cleaning of the teeth and gums, but does not accept as proved on the evidence at present available any claim that a dentifrice can actively prevent dental disease otherwise than by virtue of its function as a cleaning agent."

# COMBINED ANTIBIOTIC THERAPY FOR THE SUPPRESSION OF RESISTANT VARIANTS IN URINARY INFECTION

BY

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AND

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One of the most important problems arising from antibiotic therapy is the emergence of resistant variants. While this is most serious in chronic diseases requiring prolonged courses of treatment, the treatment of acute infections can also result in the appearance of resistant organisms. Treatment will then be ineffective, and if the organism causes infection in others it will be resistant from the start. This phenomenon is best known in connexion with the staphylococci, a large proportion of which, in hospital, are now resistant to penicillin and already show evidence of becoming resistant to the newer antibiotics.

The use of pairs of antibiotics has been investigated by most workers primarily from the point of view of their synergistic or antagonistic action against the infecting organism, but it is becoming more widely recognized that of equal if not greater importance is the ability of combined treatment to suppress the emergence of resistant variants, which, if a single antibiotic was used, would continue the infection after the elimination of the parent strain (Carpenter *et al.*, 1945 ; Dowling, 1951 ; Klein and Schorr, 1953). Such combined treatment has been particularly successful in tuberculosis, and this problem has been reviewed by Mitchison (1954).

Antibiotics are now being used extensively for the treatment of urinary infections, some 80% of which are caused by the coliform group of organisms. With these organisms it is not uncommon for treatment with a single antibiotic to fail or for a recrudescence to occur owing to the emergence of a resistant variant. This is particularly so with streptomycin ; indeed, with as many as 50% of urinary infections resistant organisms may appear and render further treatment with this antibiotic futile (Garrod, 1950). The use of the tetracyclines for urinary infections is also not uncommonly followed by the development of resistant variants (Herrold, 1951). That combined treatment might overcome these difficulties was suggested by Kaipainen (1952), who showed by means of repeated subcultures in tubes that when streptomycin was combined with either chloramphenicol or tetracycline strains of *E. coli* showed little or no increase in resistance to the antibiotics.

In urinary infections it is particularly important that effective methods of treatment should be available. Prolonged or repeated attacks are apt to lead to the development of chronic pyelonephritis with all its attendant dangers. The present work is concerned with an *in vitro* investigation of the value of combinations of two antibiotics in suppressing the emergence of resistant variants against strains of coliform bacilli isolated from cases of urinary infection. The simple technique of the gradient plate (Szybalski, 1952) was used for the investigation.

## Methods

Gradient plates were prepared as illustrated in Fig. 1. The lower layer of nutrient agar was poured into a Petri dish, which was kept on a slant so as to form a layer of diminishing thickness from one side of the plate to the other. The upper layer contained antibiotic. The concentrations were 12 $\mu$g. of streptomycin or chloramphenicol per ml., 6 $\mu$g of tetracycline per ml., or combinations of these antibiotics in the same concentrations. Streptomycin+tetracycline, streptomycin+chloramphenicol, and tetracycline+chloramphenicol were the combinations tested. The antibiotic diffuses downwards into the lower layer and within a short time there is established an even gradient of antibiotic concentration which remains relatively stable during the course of the experiment ; from 12 $\mu$g. of streptomycin or chloramphenicol per ml. or 6 $\mu$g. of tetracycline per ml. at one end of the plate to practically zero at the other end. This range of concentration was found to be the most suitable for the majority of coliforms tested, and, moreover, encompassed the levels which commonly occur in the tissues of a patient between doses of the drugs.

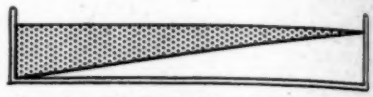

FIG. 1.—Gradient plate. The lower layer of agar is poured into a Petri dish which is kept on a slant. When the lower layer has set an equal volume of agar containing antibiotic is poured on top.

Forty-two strains of coliform bacilli obtained from urinary infections were tested ; 39 *E. coli*, 2 *A. aerogenes*, and 1 paracolon bacillus. These were grown for four to six hours in nutrient broth and the concentrations adjusted so that 0.5 ml. contained $10^8$ organisms. This population was flooded over the surface of each plate. The plates were dried and incubated for 24 hours. The number of resistant colonies on each plate was counted and a replica of the plate was then made on to a nutrient agar surface by means of the velvet-pad method (Lederberg and Lederberg, 1952), in order to assess the bactericidal effect of the antibiotics (Hilson and Elek, 1954).

## Experimental Findings

### Incidence of Resistant Variants

A typical experiment is shown in Fig. 2. When the antibiotics were used singly the lower third of the gradient plate, where the antibiotic concentration was lowest, showed diffuse growth of the organism. This area ended fairly abruptly, and above there were varying numbers of discrete resistant colonies. With streptomycin there were usually about 100 to 200 colonies in a wide zone, often extending into the uppermost segment of the plate. Only one out of 32 streptomycin-sensitive organisms showed a narrow band of colonies lying just above the line of inhibition of the parent strain. Both tetracycline and chloramphenicol showed a much smaller number of discrete colonies, usually lying just above the area of diffuse growth. With the three drugs the colonies varied in size from 1 to 2 mm. in diameter

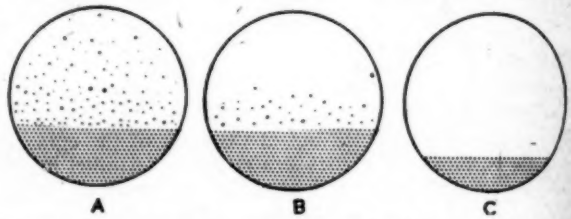


FIG. 2.—Illustrations of results after 24 hours' growth of a coliform bacillus on gradient plates. A is a streptomycin plate, B is either a chloramphenicol or a tetracycline plate, and C is a plate containing two of these antibiotics. With the single antibiotics there is diffuse growth in the lower part of the plate and, above, varying numbers of discrete resistant colonies. With the pairs of antibiotics resistant colonies are absent.

to pin-point size. All the colonies, however, had a similar degree of resistance to the antibiotics, about three to four times that of the parent organism. Table I shows the numbers of resistant colonies formed by 32 coliform strains sensitive to each of the three antibiotics.

TABLE I.—*Incidence of Resistant Variants in 32 Strains of Coliform Bacilli on Gradient Plates*

| | Streptomycin | | | Chloramphenicol | | | Tetracycline | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of variants (per $10^8$ orgs.) | 25–50 | 50–150 | 150–200 | 5–10 | 10–25 | 25–50 | 0–5 | 5–10 | 10–25 |
| No. of strains.. | 4 | 20 | 8 | 8 | 18 | 6 | 6 | 22 | 4 |

Fig. 2 (C) illustrates the results obtained with the pairs of antibiotics. The results were identical with the three combinations tested. With every one of the 32 strains that were sensitive to both antibiotics the zone of diffuse growth occurred lower in the plate, and, in fact, in most cases the plates showed no growth at all. Moreover, above the zones of diffuse growth resistant colonies were absent. Combinations of two antibiotics therefore not only had a synergistic action against the growth of the organism but also prevented the emergence of resistant variants. On the other hand, 10 coliform strains that were resistant to one or other of the two antibiotics in the combinations behaved exactly as if exposed only to the effective antibiotic.

### Bactericidal Effects

The chances of the emergence of resistant variants are closely related to the living bacterial population. It is therefore important to distinguish between bactericidal and bacteriostatic effects, and for this purpose the replica-plate method has been used. The organisms on the surface of the gradient plate, including viable but inhibited organisms, were transferred on to an antibiotic-free plate, where the viable cells could grow and form colonies. Typical results are shown in Fig. 3. Streptomycin was essentially bactericidal, the colonies present on the plate arising from organisms transferred from the already resistant colonies on the original gradient plate. Chloramphenicol and tetracycline, on the other hand, were mainly bacteriostatic, the replica plates showing diffuse growth.

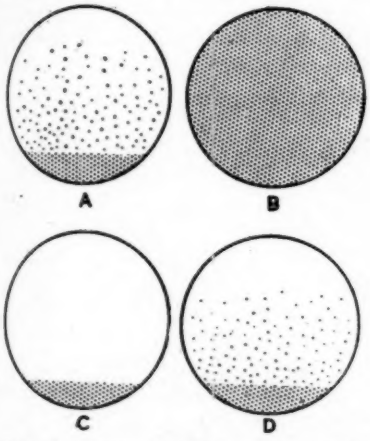


FIG. 3.—Illustrations of replica plates made from gradient plates by the velvet-pad method. The replicas show the survival of the population inoculated as against the inhibition of the population on the gradient plates. A is a replica from a streptomycin plate, B is from either a chloramphenicol or a tetracycline plate. C and D are the two kinds of result obtained with streptomycin plus either chloramphenicol or tetracycline.

With the pairs of antibiotics two kinds of results were obtained. With streptomycin + tetracycline and with streptomycin + chloramphenicol about half the organisms tested showed no growth on the replica plates. The remaining organisms showed an appearance similar to that obtained on a gradient plate containing streptomycin only. In the first case, therefore, the resistant variants had been killed by the combined antibiotics. In the second case the resistant variants had only been inhibited; the organisms resistant to streptomycin but inhibited by tetracycline or chloramphenicol multiplied to form colonies when the antibiotics were removed. The former result would seem to indicate that tetracycline and chloramphenicol may occasionally possess some bactericidal activity, having killed the streptomycin-resistant variants. Indeed, with three of our strains it was possible to demonstrate that both tetracycline and chloramphenicol, when used alone, had a bactericidal effect exceeding 99%.

Replica plates from the gradient plates containing tetracycline + chloramphenicol showed, in the majority of cases, diffuse growth, indicating that, although the resistant variants were effectively inhibited, the combination of these drugs had little or no bactericidal activity. However, with the three coliform strains against which tetracycline and chloramphenicol possessed striking bactericidal activity the replica plates showed only a scanty growth of discrete colonies. These findings indicate that generalizations about the bactericidal action of a given antibiotic are often not valid for a particular strain of organism.

### Chances Against Emergence of Resistant Variants

An attempt was made to confirm the value of antibiotic combinations for the suppression of resistant variants by observing the incidence of variants resistant to each antibiotic used separately. Populations of $10^8$ organisms were inoculated on to plates containing the antibiotics in concentrations just above the inhibitory levels and the number of resistant colonies present after 24 hours' incubation was counted. Each experiment was repeated six times from separate cultures in order to obtain the extent of the fluctuation in the numbers of resistant colonies. Table II shows the results with one of the strains of coliform bacilli. The organism was inoculated on six separate occasions on to plates containing 5 μg. of streptomycin per ml., 5 μg. of chloramphenicol per ml., and 2 μg. of tetracycline per ml. Fluctuation in numbers did occur, as expected, but the figures were not widely different. Streptomycin showed the highest number of resistant variants, averaging 50 resistant cells per $10^8$ organisms. Chloramphenicol was next with 22, and tetracycline had the lowest number with only about 6 per $10^8$ organisms.

TABLE II.—*Fluctuation in Numbers of Resistant Variants Obtained with 6 Cultures of a Single Strain of Coliform Bacillus Following Exposure to Minimum Inhibitory Levels of Antibiotics*

| | 1 | 2 | 3 | 4 | 5 | 6 | Average |
|---|---|---|---|---|---|---|---|
| Streptomycin 5 μg./ml. | 27 | 44 | 47 | 106 | 62 | 17 | 50 |
| Chloramphenicol 5 μg./ml. .. .. | 15 | 25 | 25 | 32 | 17 | 19 | 22 |
| Tetracycline 2 μg./ml. | 7 | 12 | 5 | 0 | 7 | 6 | 6 |

Two further strains tested in this way gave numerically similar results. These findings are likely to apply to all the strains used in the investigation, since all produced approximately the same number of resistant colonies on the gradient plates (Table I). In fact, although not strictly quantitative, the gradient plate gives a fair indication of the mutation rate. The majority of the strains formed between 50 and 150 resistant colonies on the streptomycin plates, between 10 and 25 on the chloramphenicol plates, and between 5 and 10 on the tetracycline plates, with a few strains forming somewhat higher or lower numbers. It is interesting that two strains which formed an unusually large number of resistant colonies on streptomycin also produced unusually large numbers of variants on both tetracycline and chloramphenicol.

The average incidence of variants calculated on the above figures for streptomycin is 1 in $2 \times 10^8$, for chloramphenicol 1 in $5 \times 10^8$, and for tetracycline 1 in $15 \times 10^8$. By simple multiplication it is possible to calculate the chance of a variant arising which is simultaneously resistant to two antibiotics. Thus, for streptomycin + chloramphenicol it is 1 in $10^{17}$, for streptomycin + tetracycline it is 1 in $3 \times 10^{17}$, and for chloramphenicol + tetracycline it is 1 in $7.5 \times 10^{17}$. It is

unlikely that a population of $10^{13}$ organisms (which would represent about 10 litres of an overnight broth culture) could be obtained in the human body during the course of an acute infection. The longer the infection persists, however, the more likely is it that sufficiently large numbers of bacteria will be concerned.

These calculations are based on the assumption that the mutation rate of an organism which has become resistant to one antibiotic does not at the same time alter towards the second antibiotic. To test this point variants resistant to one antibiotic were subcultured and the incidence of variants resistant to a second antibiotic was determined in the manner already described. It was found that in the case of all three antibiotics no significant change in mutation rate occurred.

## Discussion

Our results agree with those of Kaipainen (1952) that combinations of antibiotics are effective in suppressing the emergence of resistant variants of the coliform group of organisms, provided the organism is sensitive to both the antibiotics in the combination. The calculated chances of a doubly resistant variant arising provide theoretical support for the value of combined therapy.

There is good evidence that a bactericidal effect should be aimed for in treating urinary infections: otherwise inhibited organisms, lying protected in devitalized tissue, may cause a relapse after withdrawal of the drug (Nesbitt *et al.*, 1951; Stansfeld and Webb, 1954). Streptomycin is the only effective bactericidal drug at present available for urinary infections, but its use is notoriously apt to result in the appearance of resistant variants. Our results show, however, that when it is combined with tetracycline or chloramphenicol the bactericidal action is retained and the resistant variants are effectively suppressed. In about half the cases this suppression is complete in so far that the resistant variants have actually been killed. In the other half the resistant variants are only inhibited, and treatment must be sufficiently prolonged to allow the body defences to destroy these few remaining organisms; otherwise relapses are possible. Chloramphenicol+tetracycline is the most effective combination for suppressing the resistant variants, but with only a few strains of coliform bacilli is there adequate bactericidal action.

We have not yet carried out a clinical trial of the value of antibiotic combinations in preventing relapses, but the *in vitro* tests indicate that good results are to be expected. While this work has been concerned only with urinary coliform infections it seems likely that the results would also apply to the treatment of other infections with organisms which are capable of becoming resistant to a single antibiotic. The wider use of antibiotic combinations could perhaps avert the threat of the increasing numbers of antibiotic-resistant bacteria.

## Summary

Combinations of streptomycin, tetracycline, and chloramphenicol have been tested for their value in suppressing the emergence of resistant variants of coliform bacilli isolated from cases of urinary infection.

Streptomycin + tetracycline and streptomycin + chloramphenicol are the most effective combinations. Not only are resistant variants suppressed, but these combinations possess bactericidal activity which is probably also an important factor in preventing relapses in urinary infections. Chloramphenicol + tetracycline prevent the emergence of resistant variants but have little or no bactericidal activity against most strains.

Calculations of the chances of a variant arising which is simultaneously resistant to two antibiotics show that the efficacy of combined treatment is explained by the large size of the bacterial population required for such doubly resistant variants to arise. It is unlikely that during the course of an acute urinary infection sufficiently large bacterial populations can be attained.

It is suggested that these findings have an application in clinical practice.

We are indebted to the Endowment Fund of St. George's Hospital for a grant towards the expenses of this work. We wish to thank Professor T. Crawford for his help in preparing this paper.

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# THE "MULTIFIDUS TRIANGLE" SYNDROME AS A CAUSE OF RECURRENT LOW-BACK PAIN

BY

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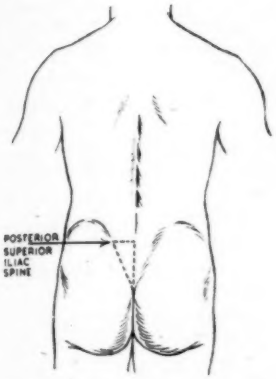
Among the many patients who have attended the department of physical medicine at St. Thomas's Hospital complaining of recurrent attacks of acute low lumbar pain, it has been possible to identify a small group with a substantially similar pattern of history, signs, and symptoms. These suggested that the cause was a lesion in the soft tissues occupying a triangular zone on either side of the posterior surface of the sacrum. Livingston (1941) described such a syndrome, and referred to the area involved as the "multifidus triangle" because in it lies the lowermost portions of the multifidus, muscle, which acts to stabilize the spine in its relation to the sacrum (see Diagram). He stressed that attacks are often brought on by physical exercise involving bending and twisting of the lumbar spine. A sharp localized pain may occur, followed by a persistent discomfort ascribed to one spot just below the posterior superior iliac spine. This ache may gradually decrease during succeeding days, so that the patient may not be particularly concerned. However, a feature of such cases is the tendency for attacks to recur after intervals of relative freedom. Steindler and Luck (1938), in a series of 451 patients suffering from low-back pain, observed that in more than 20% of these cases it was possible to demonstrate a local point of tenderness situated in the deeper tissues. They were of the opinion that the lesions represented either a deep ligamentous injury or a myofascial lesion. The work of Lewis and Kellgren (1939) suggests that such a focus may result in

both deep and superficial tenderness, and radiation of pain to buttocks and thighs, with or without muscle spasm.

In sufferers from the "multifidus triangle" syndrome type of low-back pain and disability not only is there a demonstrable point of local tenderness but pressure over this area usually aggravates the pain and causes some radiation in the distribution remarked on in the patient's history. Livingston (1943) treated such cases with local injections of 2% procaine solution into the sensitive "trigger" points, and obtained eventual relief from signs and symptoms after several consecutive injections.

It was considered that the injection of a mixture made up of hydrocortisone, hyaluronidase, and procaine into the tender area localized in the "multifidus triangle" might give quick and long relief to the patient. The rationale was that the procaine would afford relief from pain if the trigger zone had been accurately located, and that the anti-inflammatory fibrinolytic action of the hydrocortisone together with the spreading action of the hyaluronidase might make the effect permanent or more durable.




The dotted lines demarcate and show the position of the "multifidus triangle," which presents as an inverted right-angled triangle whose base extends from the midline to the posterior superior iliac spine and whose apex is at the lowermost point of origin for the multifidus muscle.

### Selection of Cases

All patients were examined thoroughly and the lumbar spine and hip-joints were *x*-rayed, following the routine used by Coyer and Curwen (1955). This consisted of a detailed history regarding possible trauma and attacks of pain, and any signs of skeletal, joint, or neurological significance. The salient features noted in the examination were as follows: (1) the site of the pain, (2) whether there was any radiation of pain, (3) whether there was any restriction of lumbar spine movements or straight-leg raising, and (4) the presence of any neurological signs in the lower limbs.

Thus 20 patients in all, 14 of whom were females, were found to be suffering from the "multifidus triangle" syndrome. All complained of dull pain localized to one or other side of the lower lumbar area; this was intermittent in character, and made worse by excessive bending or lifting, so that the pain became more acute and occasionally radiated to one thigh or buttock of the same side. Occasionally coughing made the pain worse, but all patients experienced relief on resting in bed. Ten of the cases gave a definite history of trauma involving bending and lifting, which they thought had started the trouble.

On examination two positive signs were found in all cases. Firstly, there was the complaint of increase in the localized pain on lumbar spine extension, or a painful arc on extending from the flexed position. With the patient lying prone, resisted lumbar extension also increased the pain. Secondly, on palpation a localized tenderness could be demonstrated in the "multifidus triangle" on the affected side with a degree of pressure which did not produce pain in a corresponding site on the normal side.

The negative signs also are of interest. The rest of the lumbar spine movements were full and complete, except in one case of recent and acute onset after trauma, when lateral flexion to the painful side was also painful. Straight-leg raising was full and complete in all cases. Radiological examination revealed nothing abnormal except slight osteophytic lipping in some of the older patients, nor were any neurological signs elicited.

The history of pain and disability varied from two years to one month, and in the majority of cases was intermittent in character.

### Technique

In each case the point of maximum tenderness or trigger zone was determined in the "multifidus triangle," with the patient lying in the prone position. A skin pencil was then used to mark the surface directly over the painful spot. A mixture of 50 mg. of hydrocortisone in a 2-ml. suspension, with the addition of 1,000 units of hyaluronidase and 3 to 4 ml. of 1% procaine hydrochloride, was then injected deep into the tender spot, using the skin marking as a guide. In most cases the patient complained of increased pain and radiation, as the tender focus was irritated by the needle. This, of course, helped accuracy of location before actual injection of the mixture was made. The patient was allowed to rest for 15 minutes, and then re-examined regarding degree of pain, tenderness, and range of lumbar spine movement. Every case showed improvement, though most still had a slight dull ache on the affected side. There was no increased tenderness on pressure, and resisted lumbar extension did not increase the pain. All the cases were re-examined at weekly intervals for one month. Fifteen were symptom-free and had no signs of tenderness in the "multifidus triangle," and there was a full range of lumbar spine movement after one week.

Two patients required a second injection after one week because there were still tenderness and restricted painful movements on extension of the lumbar spine.

At the end of four weeks all patients were symptom-free and had normal spinal movements and no evidence of tenderness (see Table).

*Results*

| No. of Cases | Improved Immediately After Injection | Well in 1 Week | Required 2nd Injection After 1 Week | Well in 4 Weeks |
|---|---|---|---|---|
| 20 | 20 | 15 | 2 | 20 |

The patients have been instructed to let us know if they have a recurrence of trouble. To date, for a period of three to six months, there have been no recurrences.

### Summary and Conclusion

The "multifidus triangle" syndrome is described as a cause of localized low-back pain, often with acute episodes and characterized by a tender focus or "trigger" zone.

The condition is probably due to deep ligamentous or myofascial injury, which may be exacerbated by recurrent trauma.

Twenty such cases were treated by injections of a mixture of hydrocortisone, hyaluronidase, and procaine hydrochloride, resulting in complete recovery within four weeks; 18 cases required one injection only.

The injection of this mixture into tender trigger zones localized to a "multifidus triangle" is a quick and easy method of affording relief in the type of case described. In some patients this occurred after they had suffered disability with acute episodes for as long as two years, and received various treatments, including manipulations, deep heating, and massage, without relief.

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# INTRA-ARTERIAL THIOPENTONE

## REPORT OF A CASE

BY

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Thiopentone sodium (sodium ethylmethylbutyl thiobarbiturate) was synthesized by Volwiler and Tabern in 1932. Since its first introduction into clinical practice by Lundy in 1934, it has been used by the medical profession throughout the world, particularly as an intravenous agent in anaesthesia.

Cases of accidental intra-arterial injection have been reported in the literature from time to time, the position being well reviewed by Cohen (1948) in a study of 12 cases, 8 of them previously unpublished. As Sir Robert Macintosh has stated on more than one occasion, the repetition of these mistakes can be avoided only by reporting the details of any such misfortune.

### Case Report

A healthy young man aged 19 was admitted for circumcision. Premedication consisted of papaveretum, 1/3 gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.).

At 10 a.m. on May 21, 1955, anaesthesia was induced with 5% thiopentone solution, injection being made into the left median cubital vein on the anterior aspect of the upper forearm. Injection of 1 ml. was followed by the usual pause, during which the patient was asked whether he felt any pain in the forearm or hand (a routine precaution); on receiving a negative reply a further 5 ml. was injected. At this point he complained of a burning sensation, rapidly intensifying, in his forearm and hand, the severity of which caused him to writhe in agony on the trolley, to an extent requiring forcible restraint. The onset of narcosis was significantly and obviously delayed, but apart from slight flushing of the hand, especially the fingers, there was no other visible abnormality at this stage. Anaesthesia was continued, using cyclopropane and oxygen on a closed circuit with carbon dioxide absorption, and a brachial plexus block was immediately performed, using lignocaine 2% (20 ml.) and 1% (10 ml.). On completion of the block 5 ml. of 1% lignocaine was injected into the subclavian artery. The surgeon was requested to ensure complete haemostasis in view of the forthcoming heparinization.

On return to the ward further treatment was carried out as follows: (1) Heparinization: 10,000 units intravenously and repeated six-hourly; (2) sedation: morphine, 1/6 gr. (11 mg.) six-hourly; (3) elevation of limb, which was swathed in cotton-wool.

On examination of the limb the success of the brachial plexus block was confirmed by the presence of both motor and sensory paralysis with satisfactory vasodilatation, the limb being warm and pink; both radial and ulnar pulses were present. At the site of injection a superficial ulnar artery was palpable, pulsation being visible on closer inspection; this vessel was palpable for approximately 2½ in. (6.3 cm.) into the forearm. A corresponding artery in the right forearm was palpable for six inches (15 cm.).

At 2.30 p.m. the brachial plexus block had worn off. The skin temperature of the left hand and forearm was much lower than that of the right, with pallor of the digits and an increased arteriolar capillary refill time. The ulnar pulse was barely palpable on the affected side. There was no evidence of oedema of the hand or forearm. The following measures were carried out: (1) Brachial plexus block was repeated, using 50 ml. of 1 in 1,500 cinchocaine; paraesthesiae were elicited. (2) Intra-arterial tolazoline ("priscol"), 50 mg. in 1% solution, and heparin, 5,000 units, were injected into the subclavian artery. (3) Local infiltration of the left antecubital fossa and upper forearm along the course of the superficial ulnar artery, using 20 ml. of 0.5% lignocaine with 1,000 units of hyalase. The effect of this procedure was to produce again a very satisfactory vasodilatation with a warm pink limb, the condition of which remained unchanged well into the following day.

At 6 p.m. on May 22 there was a bluish discoloration of the skin in the left antecubital fossa irregularly distributed around the superficial ulnar artery, the patch having a crenated border and being surrounded by an area of pallor. The limb otherwise was warm and pink, with palpable radial and ulnar pulses. Oral tolazoline, 25 mg. six-hourly, was begun, the limb being kept under the closest observation. Subsequently the patch began to fade after three days, and the patient was finally discharged from hospital on the thirteenth day after operation. He was seen again as an out-patient 10 days later, when the condition of the limb was satisfactory.

### Discussion

The incidence of accidental intra-arterial injection of thiopentone has been variously given as 3 in 25,000 (Lundy, 1942) and 1 in 55,000 (Cohen, 1948).

When such a mishap occurs it is essential to appreciate the significance of the catastrophe. Of 12 reported cases, 6 required arm or forearm amputation, 2 suffered loss of one or more fingers, and 2 suffered severe residual disability from nerve effects. The immediate sequel to this mishap is an intense arterial spasm, especially of the distal arteriolar tree, with possible trapping or delay of some of the solution. Such spasm may persist for at least 24 hours, and is very easily precipitated when injection has been made into a superficial ulnar artery, as these vessels are derived from the vasa aberrantia, and, like other superficial vessels, have a fuller nerve supply than the deeper branches. Thrombosis is the essential pathological lesion, although it is not yet clear why the arterial tree should show such a vigorous reaction when venous thrombosis is relatively uncommon. Thiopentone is a strongly alkaline irritant, and the intima of the artery appears to be particularly sensitive to solutions of such high *p*H; a further factor may be the resistance of the arterial wall due to the relative abundance of muscle and elastic fibres. The injection of 10% solution is of much graver prognostic significance than either the 5% or 2½%. In eight of the published cases, gangrene occurred in four, and in three of these a 10% solution had been employed.

The ease with which the catastrophe may occur has been aptly described by Cohen, and his words are particularly applicable to this case when he states: "There may be little groping for the vein and the injection has often been particularly easy. Intra-arterial puncture is not followed, as is commonly imagined, by a gush of blood blowing off the syringe piston. Nor is the crimson livery of arterial blood readily discerned in the yellowish solution."

The use of a safety pause after injection of a certain amount of solution should be obligatory. It would appear, however, that the test injection of small amounts up to 1 ml. of 5% solution, as commonly recommended, is not wholly reliable, and it is suggested that 2 ml. would provide a more reliable test injection.

The pain produced on intra-arterial injection is agonizing and of a characteristic burning nature well described as a sensation of the hand being on fire. In the present case the patient on leaving hospital 14 days later could still vividly recall the burning nature of the pain in his left forearm and hand. This pain, together with the very obvious delay in the onset of narcosis, should make recognition of the accident a certainty and convince even the most obtuse of the mishap.

Once the accident has occurred the operation should be abandoned if at all possible, as the subsequent heparinization, with risk of haemorrhage from the operation site, otherwise proves a constant source of anxiety.

The presence of palpable radial and ulnar pulses does not exclude the possibility of severe damage to the intima and

subsequent thrombosis. The pulse may disappear after a few hours, or it may remain full until shortly before the onset of gangrene, as shown in three published cases, where gangrene ensued after disappearance of the pulse on the eighth, tenth, and sixteenth days, respectively. In these circumstances the only answer to this condition, once it has occurred, is intensive treatment, the necessity for which remains undiminished by the presence of palpable pulses in the affected limb.

The appearance of discoloured skin patches in the affected limb has been described in several of the previously reported cases. They have also been reported as a complication of arteriography and ascribed by Wagner (1944) to secondary spread of thrombosis from the main vessel to distal cutaneous branches. In the present case, however, with no brachial artery thrombosis, the patch would seem to have been due to a direct local effect of the thiopentone shunted into the skin vessels.

The treatment of this condition is directed towards ensuring full vasodilatation of the limb with obliteration of all arterial spasm, the prevention of thrombosis, and satisfactory venous drainage. There is no place for complacency: once the mistake has been recognized, treatment must be started immediately and followed through intensively. The experience gained from the present case emphasizes the fact that, if at all possible, the operation should not be allowed to continue, as was permitted in this instance and subsequently regretted when oozing from the penis became an additional source of worry on the second and third days.

As the patient is unconscious when the first brachial plexus block is performed immediately after the accident, and consequently paraesthesiae or other corroboration of the success of the block cannot be obtained, it is advised that Patrick's method be employed, using at least 20 ml. of solution, preferably with hyalase. The repetition of the block in the present case, several hours later after heparinization had begun, together with the intra-arterial injection of tolazoline and heparin, was recognized as a hazardous procedure, but it was felt that the vascular supply to the limb at this stage was jeopardized to a precarious extent by the arterial spasm.

Tolazoline has been the subject of a report on peripheral vascular disease by Edwards *et al.* (1952). These workers found it to be one of the best vasodilators available, and recommended a dosage of 50–100 mg. at weekly intervals. In addition, they state that "Swan's plethysmographic studies (quoted by Lynn, 1950) demonstrated an increased blood flow in an already sympathectomized limb following the intra-arterial injection of 50 mg. of tolazoline." This drug would thus appear to have properties of much value in the treatment of cases of intra-arterial thiopentone, not least of which is its prolonged action after intra-arterial injection. It is of interest to note that the same workers showed that intra-arterial procaine had little or no value in producing an increase in peripheral limb blood flow. It is suggested, therefore, that immediate treatment for cases of accidental intra-arterial thiopentone should include intra-arterial tolazoline, in addition to the brachial plexus block, a procedure easily accomplished, as Dundee (1953) states, by puncturing the subclavian artery on completion of the block. In the case under review tolazoline was not immediately available, but when it was injected into the subclavian artery the vasodilator response was both dramatic and prolonged.

Other methods of assisting vasodilatation and forcing the collateral circulation should be employed, especially warmth and sedation. The use of morphine has been shown by Learmonth (1946) to relax vessel spasm, although in the present case vomiting became a troublesome complication, which ceased on the substitution of pethidine.

In view of reports of delayed onset of gangrene in several cases, it is difficult to say for how long these measures should be maintained. In the present case the strict regime was not relaxed until the sixth day, and the patient remained under observation until the thirteenth day. By this time the danger from arterial spasm is well past, and, in the absence of any significant sign of impaired limb blood flow, it is difficult to conceive the danger of delayed thrombosis being anything but remote.


### Summary

A case of accidental intra-arterial injection of thiopentone is reported with a description of the treatment employed.

A test injection of 2 ml. with a safety pause is advocated as a preventive measure.

The operation should be abandoned, if at all possible, once the mishap has occurred.

The necessity for immediate and intensive treatment is stressed.

The use of intra-arterial tolazoline is recommended.


I wish to thank Dr. A. C. Forrester for permission to publish this case, and to express my appreciation to Professor W. A. Mackey for his advice.


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# TOTAL PAROTIDECTOMY WITH PRESERVATION OF FACIAL NERVE

## A REVIEW OF 47 CASES


BY

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The operation of total parotidectomy with preservation of the facial nerve for non-malignant conditions as advocated by Hamilton Bailey (1941) is slowly gaining adherents in this country, and 47 patients who have had this operation have now been followed up to try to ascertain the answers to three questions: (1) Does total removal of the parotid gland reduce the number of recurrences which follow local removal of mixed parotid tumours? (2) Can total removal of the parotid gland be performed and full function of the facial nerve be preserved in every case? (3) What is the cause of the Frei syndrome and how may it be prevented?

The technique of the operation used in these cases has been described elsewhere (Kidd, 1950, 1953), and the value of starting the dissection by locating the branch of the cervico-facial nerve going to the lower lip is confirmed. Increased familiarity with the operation favours the preservation of the branch of the great auricular nerve going to the lobe of the ear and, in many cases, deliberate resection of the auriculo-temporal nerve.

### Diagnosis

It is not perhaps generally recognized how many different primarily non-malignant conditions arise in the parotid gland, nor how difficult it can be to be sure that a tumour in the parotid area is actually in the gland. Many true parotid tumours feel very superficial and mobile, and deep-seated tumours may be found to arise from deep lymphatic glands. The history and careful palpation are the best guides; good sialograms are also of value, but in some cases only exploration will clinch the diagnosis. As the danger of cutting into a mixed parotid tumour is very real, it is wise to plan the incision and approach, in a difficult

case, so that total parotidectomy can be proceeded with should the tumour be found to arise from the parotid gland. Lipomas may be superficial and arise in the fat between the parotid gland and the skin, but can also lie deep in the substance of the parotid gland. Sebaceous cysts may be mistakenly diagnosed when a cystic tumour of the parotid gland is present. Pre-auricular adenitis can cause difficulty, but the length of history is usually much less than in true parotid tumours.

The 47 cases (18 male and 29 female) were made up as follows: 3 chronic infection, 2 calculus, 1 tuberculosis, 1 oncocytoma, 2 adenolymphoma, 1 lipofibromatosis, 1 lipoma, 29 mixed parotid tumour, 3 carcinoma, 2 recurrent tumour, 1 congenital fistula, and 1 cyst, of branchial origin.

The carcinoma cases included here were those found to be so on pathological examination, but, except under unusual circumstances, preserving the facial nerve is not advised when the clinical appearance indicates malignancy.

The recurrent tumours occurred in cases in which a local removal of a mixed parotid tumour had been done elsewhere, and in both the recurrence showed microscopical evidence of malignancy.

Two other cases that were obviously malignant, and were not included in this series, gave a history of a local removal of a mixed parotid tumour many years previously. The recurrence rate after local excision or simple enucleation of mixed tumours has been variously stated by different authors to vary between 10 and 30%. Irradiation has no place in the treatment of these tumours, as it never causes the disappearance of the tumour, only a reduction in size. While the natural history of mixed tumours shows that they grow slowly over many years, they are liable to sudden increases in size and malignant change. In one case, not included in this series, a girl of 16 had a mixed parotid tumour treated by local excision, and when it recurred shortly afterwards radiotherapy was given. Within a few months it had ulcerated through the skin, and in spite of wide excision, including a block dissection of the neck, death occurred nine months later. Apart from the danger of recurrence, local excision is too often followed by partial or complete facial palsy.

### Recurrence

The first case in this series was done in 1943 and the last in February, 1955, and there has been no recurrence in any of the primary cases, although two of the patients have since died of other diseases. The two recurrent cases previously mentioned, both adenocarcinoma after local excision of a mixed tumour, were treated by total excision of the gland, and the facial nerve was preserved. Two small tumours 4 mm. in diameter have been removed from one of these cases since, but there has been no further trouble during the last fourteen months. There have been no cases of permanent facial paralysis. Lower-lip palsy is present in a few cases, but was due to deliberate division of the lower branch of the cervico-facial nerve. This small series thus agrees with those of Redon (1953), of Paris, who, using a similar technique, reported 165 cases of mixed parotid tumour with no recurrence and no facial paralysis, and Patey (1954), in a recent review, also concurs.

### Frei Syndrome

The scar—if made below the jaw, in the skin crease, and curved round the lobe of the ear to split the tragus—is unobtrusive. There is, however, one sequela which may come on from one month to two years after the operation, and that is the Frei syndrome. This consists of flushing and sometimes sweating on the same side of the face as the operation, and occurs during or after a meal. It occurred in 11 out of 45 patients followed up in this series, and varied in intensity from a minor degree of flushing and dampness to a considerable discharge of sweat. About the same incidence of this syndrome is given in other reports of this operation, and no really satisfactory explanation of its cause has been given. It does not disappear spontaneously and is not easily treated. It occurs chiefly in the malar area, which is supplied by the sensory branch of the auriculo-temporal nerve. The auriculo-temporal nerve is also the motor nerve to the parotid gland, and it is thought that when the tongue is stimulated by hot or strongly flavoured substances the impulses pass via the glossopharyngeal nerve to the otic ganglion and thence to the auriculo-temporal nerve. The divided motor branches of this nerve then anastomose with the distal branches of the sympathetic system which supply the skin and which were severed when the skin flap was raised. Redon always ligates the external carotid artery, but has a 25% incidence of Frei syndrome. Although in this series it has rarely been necessary to tie this artery the incidence of Frei syndrome is about the same.

In one case in 1951 the nerve was identified and carefully preserved; this patient developed a Frei syndrome. Since 1951 an attempt has been made to identify the auriculo-temporal nerve, and in 10 cases in which it was thought to have been clearly identified and sectioned, as far proximally as possible, only one has developed a complete Frei syndrome and one has a flush only.

### Conclusion

The results of this review allow the questions posed at the beginning of this paper to be answered as follows:

1. The recurrence rate for mixed parotid tumours can be reduced to nil by total parotidectomy, with preservation of the facial nerve.

2. The facial nerve can be preserved and will recover its functions in every case.

3. The cause of the Frei syndrome is not known, but deliberate identification and resection of the auriculo-temporal nerve may materially reduce the 25% incidence of this complication.


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# Medical Memoranda

## Perforation of Intestine by Unsuspectedly Swallowed Foreign Body

It must be quite unusual to find, during laparotomy, intestinal perforation caused by a foreign body the patient did not know had been swallowed. The following three cases occurred in the Royal Alexandra Infirmary, Paisley, during 1954.

### Case Reports

*Case 1.*—A woman aged 43 had rheumatoid arthritis, and was in the orthopaedic ward just recovering from an osteotomy of the neck of the femur, when she developed severe pain in the left side of the abdomen with nausea and slight pyrexia. On examination she had marked tenderness and rigidity in the left iliac fossa, suggesting local peritonism or peritonitis. Without rectal and vaginal examination, which could not be made owing to the orthopaedic condition, a twisted ovarian cyst seemed a possible diagnosis, and laparotomy was indicated. At operation there was a mild peritonitis with slight turbid exudate, and a splinter of wood 1½ in. (3.8 cm.) long was found perforating the middle of the small intestine. It was removed and the puncture holes—then almost invisible—were closed. Convalescence was uneventful. The patient did not remember swallowing the splinter.

*Case 2.*—A woman aged 47 complained of having had pain in the right iliac fossa for 24 hours, with nausea. Her temperature was 99.2° F. (37.3° C.). There was moderate tenderness and slight rigidity in the right iliac fossa, and the condition appeared to be acute appendicitis, but at operation the appendix was normal, and a splinter of wood 1½ in. (3.8 cm.) long was found perforating the bowel at

its mesentery, which was rather indurated. The foreign body was 6 in. (15 cm.) from the ileo-caecal junction. There was no evidence of diffuse peritonitis. The splinter was removed and the patient made an uneventful recovery. She had no recollection of swallowing the splinter.

*Case 3.*—A man aged 34, an epileptic, had had appendicectomy performed elsewhere in 1952. Since then he had constant, sometimes severe, pain in his scar, and by 1954 he was showing signs of an incisional hernia, for which he was admitted. At operation the scar tissue was peculiarly oedematous and appeared almost cartilaginous, and deep in the wound was found a spicule of bone 2½ in. (6.3 cm.) long penetrating from adherent small intestine into the abdominal wall. Owing to the danger of infection, which subsequently developed, the hernia was not repaired at this time, but was dealt with successfully later. He had no recollection of swallowing this bone. The interesting point arises, whether or not the bone was the cause of the original complaint (as in Case 2 above). One cannot be conclusive, but the history of constant pain since the original operation is suggestive.

### Comment

It is not suggested that this condition should be kept in mind in the differential diagnosis of every "acute abdomen," but it could be remembered with profit during laparotomy, when the pre-operative diagnosis proves wrong and nothing else can be found. If the foreign body be overlooked the abdomen may seem quite normal, as there may be no evidence at that time of diffuse peritonitis.

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## Stokes–Adams Attacks in Bundle-branch Block

"People with heart disease do not faint." Exceptions to this valuable general rule are few. Severe aortic stenosis may be a cause of syncope of exertion, if the stenosis is severe and the heart muscle not too good. Auricular flutter may cause syncope from cerebral anaemia during short periods of 1:1 block, when the heart rate is raised to a high figure and the cardiac output becomes uneconomic. Myocardial infarction, where shock is severe, is a cause of unconsciousness. Since Stokes's original description in 1854, Stokes–Adams attacks have been a well-recognized cause of sudden, brief, and total unconsciousness. Stokes–Adams attacks are presumably due to involvement of the idioventricular pacemaker, at the upper part of the bundle of His, in the pathological lesion which is causing the heart-block. This association is well recognized in complete or partial auriculo-ventricular dissociation. There is no logical reason why such a pathological lesion should not be so placed in the bundle of His that it causes permanent bundle-branch block, transient heart-block, and infiltration of the auriculo-ventricular node to an extent sufficient to produce Stokes–Adams attacks during such transient heart-block. This possibility, so far as I am aware, was first envisaged and described in a communication I made to the British Cardiac Society in 1948, but which was not published. The following paragraphs summarize this communication.

*Case 1.*—This patient was a man of 70 who, for seven months previously, at intervals of a month or less, had frequent attacks of syncope. These were abrupt in onset, lasted three to five seconds, and were not followed by headache, drowsiness, or any other sequelae. He was just as well after the attacks as before. The heart showed moderate enlargement on cardioscopy. There was a harsh systolic murmur at the apex base. The heart rate was 56 and was regular. The blood pressure was 116/72. The cardiogram showed a P–R interval of 0.2 second and a prolonged QRS complex, with evidence of right bundle-branch block. He was given ephedrine, ½ gr. (32 mg.) thrice daily, and from that day, a period of twenty-one months, has remained free from attacks.

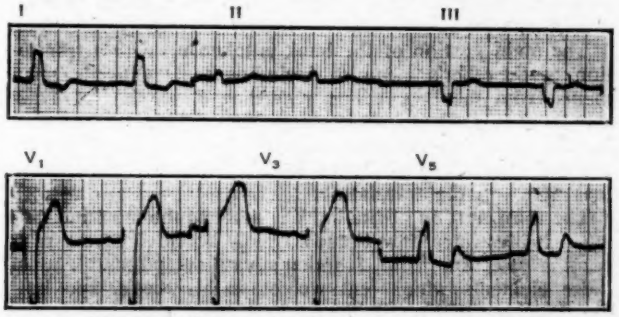
*Case 2.*—A woman of 61 had a two-years history of from four to eight weeks' interval between attacks, the frequency of which had increased for a month or two previous to examination. The attacks were abrupt and were not followed by sequelae, nor were they preceded by any warning. They lasted ten seconds, for the husband was in the habit of counting ten seconds, by which time he knew that his wife would recover. She had been thoroughly investigated for epilepsy. There was an aortic systolic murmur. The blood pressure was 150/90. The cardiogram showed an increased P–R interval of 0.23 second and bundle-branch block. Cardioscopy showed moderate enlargement. Further tracings taken to exclude a previous infarct were done, and in two of these a transient true heart-block, with dropped ventricular beats, was shown.

Both of these patients had a history of attacks of unconsciousness of abrupt onset, lasting for a few seconds only, and not followed by any headache, disorientation, drowsiness, or other sequelae suggesting epilepsy. In both cases there was evidence of a bundle-branch lesion. In each case the administration of ephedrine eliminated the attacks, which had previously been frequent. A third similar case is now reported.

### Case 3

A man aged 55, with no significant past or family history, had for three years previous to examination been conscious of a sudden feeling lasting for a few seconds, which would "well up" and cause him to feel dizzy and lost. In a number of them he had in fact abruptly and completely lost consciousness. He had stopped driving his car and riding. He had not suffered from dyspnoea, coronary symptoms, or other cardiovascular complaints. His work was journalistic and sedentary.

On examination he looked well. The heart rate was 60, the rhythm was regular, the blood pressure was 180/98. The heart sounds were clear and normal. There were no basal rales. The liver was not enlarged. There was no oedema of the legs or feet. The electrocardiogram was that of classical complete left bundle-branch block (see Fig.). Radiologically the heart was normal in size and shape, the transverse diameter by orthodiagraph being 13.3 cm.




Case 3. Electrocardiogram showing complete left bundle-branch block. Leads I, II, III, $V_1$, $V_3$, $V_5$.

The diagnosis of Stokes–Adams attacks was made in an individual free from auriculo-ventricular dissociation, but with a left bundle-branch block. Ephedrine, ½ gr. (32 mg.), three times a day after meals, was advised, the dose if necessary to be raised to 1 gr. (65 mg.) three times a day after meals. Five months later his general physician wrote as follows: "Ever since the ephedrine tablets have been taken regularly the attacks have stopped completely. Prior to this, of course, he had thirty to forty attacks during the previous two years. I thought you would like to have this interesting news of the patient."

### Comment

The differential diagnosis of such cases, in view of the abruptness of the attacks and the complete unconsciousness, must lie between epilepsy, symptomatic or idiopathic, and unusually abrupt vasovagal syncope. The presence of a bundle-branch lesion should always rouse suspicion that the attack may be due to Stokes–Adams syndrome. In all three cases I have mentioned a therapeutic dose of ephedrine has both confirmed the diagnosis and freed the patient from an unpleasant symptom.

GEOFFREY BOURNE, M.D., F.R.C.P.

# Reviews

## SCHREBER'S MEMOIRS

*Memoirs of My Nervous Illness.* By Daniel Paul Schreber. Translated, edited with introduction, notes and discussion by Ida Macalpine, M.D., and Richard A. Hunter, M.D., M.R.C.P., D.P.M. (Pp. 416; illustrated. 35s.) London: Wm. Dawson and Sons Ltd. 1955.

Daniel Paul Schreber, "the most frequently quoted patient in psychiatry," was a President of a Court of Appeal and a learned and cultured man. He suffered twice from mental illness—from severe hypochondriasis in 1884 and from a paranoid illness from October, 1893, onwards. He was a patient at the Sonnenstein Asylum, Saxony, for almost nine years, when he succeeded, though still ill, in having his tutelage rescinded. Schreber's memoirs are of this latter illness. They were published in 1903 and may well have passed into oblivion, especially as most copies were bought up and destroyed by his family. However, Freud applied the method of psycho-analysis to the material in Schreber's memoirs, and in 1911 published his "Psycho-analytical Notes upon an Autobiographical Account of Paranoia (Dementia Paranoides)," in which he explained paranoid symptom-formation by conflict over unconscious homosexuality.

The present publication may be divided into three sections. There is an excellent introduction, weakened only by some irrelevant remarks regarding physical methods of treatment.

The authors apparently believe that psychological illness should, *a priori*, be treated only by psychological methods. This is an attitude which presumes a body–mind duality, and if persisted in would have the effect of making psychiatry a separate discipline from, rather than a part of, general medicine.

The main portion of the book is taken up with a translation of Schreber's memoirs, including the "Official Documents from the Proceedings regarding Rescission of Tutelage." This difficult task has been well done, and the result is clear and readable. The memoirs themselves are fascinating, even the "Official Documents." There are some excellent notes on the translation.

The third portion of the book is perhaps the most interesting. It illustrates how Freud's widely accepted theory rests upon a selection from Schreber's vast symptomatology of those elements which lent weight to his thesis, and how the criticisms of Freud's theory have been essentially irrelevant because the bases of the criticisms have been, not Schreber, but Freud's selections from Schreber. The authors also put forward their views of the psychopathology of Schreber's illness. They are modest enough to avoid giving a theory of the aetiology of all paranoid illness from an analysis of a single case. There are, however, statements in this section which one would question—for example, that there is "confusion about their own sex invariably found in schizophrenics." Moreover, it is suggested that to confront a paranoid patient "with his anxiety and depression in terms of uncertainty in his own identity, to try to understand and trace out such body fantasies with him, often leads to amelioration of symptoms, sometimes surprisingly quickly." This is an astonishing and, if verified, very important statement; it deserves to be critically evaluated rather than thrown out as an incidental remark.

Schreber's memoirs are of interest to psychiatrists for their intrinsic merit and because they enable the bases of "Freud's brilliant analysis" to be truly evaluated. The authors have rendered a great service by making them more readily available and in so readable a form.

A. W. BEARD.

## PATHOLOGY ILLUSTRATED

*Color Atlas of Pathology.* Volume II. Prepared under the auspices of the U.S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. (Pp. 450+x; 1,032 figures in colour on 343 plates. £7.) Philadelphia, London, Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Company Ltd. 1954.

This is the second volume of a remarkable work which will be completed when a third volume, now being compiled, is published. The present book deals with diseases affecting the endocrine system, the organs of the female and male generative system, the mammary gland, and the skin. These subjects are illustrated by well over a thousand photomicrographs and photographs of naked-eye lesions, in all of which colour has been most faithfully rendered.

It was pointed out in the review of the first volume (*British Medical Journal*, 1951, **2**, 653) that the high standard of the photography accentuated every imperfection in the selected material. This criticism applies to the present work, but the high average standard of reproduction of both macroscopical and microscopical appearances places it in the front rank of pathological atlases, in which the skilled artists of other days are totally replaced by the many devices which modern photography has to offer. It remains an open question whether photography can always replace the masterpieces of a talented artist with long experience in pathological illustration.

G. HADFIELD.

## TEXTBOOK OF OBSTETRICS

*Obstetrics.* By J. P. Greenhill. 11th edition. (Pp. 1,088+viii; illustrated. 98s.) Philadelphia and London: W. B. Saunders Company. 1955.

The fame of Chicago obstetric medicine was spread abroad for more than a quarter of a century by DeLee, and his mantle has fallen on the worthy shoulders of Greenhill. Williams's *Obstetrics* is the only other comparable book published in the United States of America. The author states that "the entire book has again been rewritten" (with the aid and advice of a panel of experts) since the tenth edition four years ago; and when it is recollected that there are over a thousand pages, some idea is obtained of the work involved in writing a successful textbook.

Such a volume can be written either by a number of obstetricians, each writing on some branch of which he is an acknowledged authority, or by a single individual aided by colleagues. The first type possesses undoubted authority, but lacks cohesion and homogeneity. The second is more personal and is an entity, but suffers from the inherent defects of trying to present varying viewpoints impartially, and from consequent misrepresentations. Further, it is difficult to rewrite one's own chapters, and modern views tend to become mixed with old ideas, so that the whole chapter sometimes appears contradictory.

Seven entirely new chapters are included: on roentgenology in obstetrics, analgesia and anaesthesia, foetal erythroblastosis and the Rh factor, diseases of the nervous system, induction of labour, and endocrine changes and diseases during pregnancy. Generally speaking these are not so good as the former chapters, and the last contains a number of equivocal statements. Two columns of print occur on each page, giving it the appearance of a journal. The book is profusely illustrated, all the illustrations being of the standard one expects in an American book.

This important textbook contains a vast amount of valuable information and represents prodigious efforts on the part of a world-famous obstetrician who succeeds in stamping his personality on every chapter. It would be as impossible in the space of a short review to indicate the scope of this work as it would be ungenerous to indicate some of its defects. The best tribute that your reviewer can make is to express his regret that no such book has ever been published in England.

G. W. THEOBALD.

## CARDIOVASCULAR DISEASES

*Heart—A Physiologic and Clinical Study of Cardio-vascular Diseases.* By Aldo A. Luisada, M.D. Foreword by Herrman L. Blumgart. Second edition. (Pp. 680+xiv; illustrated. £5 14s.) London: Baillière, Tindall and Cox. 1954.

To read the table of contents of this book is at once stimulating and novel, for the headings show that an original point of view may be expected; and this proves to be the case. The brief historical chapter is useful in giving some idea of chronology. The chapter on physiology is very well done and forms a good foundation. In the clinical study, as one has so often noted, the interrogation of the patient as to the symptoms, and how full understanding and knowledge of these experiences is gained, receive but little attention. For instance, dyspnoea has only ten lines or so in a half-page column, and palpitation, which oddly enough comes first, has only thirteen. The simple clinical study of the veins in the neck receives little attention, but the phlebogram, unlikely to be taken, has pages of print devoted to it. All technical procedures are clearly described and critically assessed. The short chapter on the classification of disease is very useful. Throughout expression is direct and brief—sometimes too short, so that there are important omissions. For example, in one place the reader might think that the paradoxical pulse occurred only with a constricted pericardial sac.

Advice on treatment is good; the action of the various drugs is clearly described, but the methods of their administration might be more fully explained. Each chapter has a large number of references, conveniently referred to in the text by numerals. Many of the illustrations are rather crude and ill drawn, if not inaccurate. The picture of the man in an attack of angina hardly conforms to the usual gesture patients use to locate their pain; the dramatic illustrations of the drug merchant that appear in the journals are much better. Nor does Fig. 257 suggest that the pain spreads to the jaw. Much of the author's individual opinions are given well-deserved space. This book is throughout full of information of the best and most up-to-date kind.

TERENCE EAST.

## ARTIFICIAL LIMBS

*Human Limbs and Their Substitutes.* By Paul E. Klopsteg, Ph.D., Sc.D., Philip D. Wilson, M.D., *et al.* (Pp. 844+xiv; illustrated. 96s.) New York, Toronto, London: McGraw Hill Book Co., Inc. 1954.

After the second world war the United States Government allotted large sums of money for the investigation of human locomotion and research on artificial limbs. This they did at the instigation of the Veterans Administration. Surgeons, engineers, and scientists attached to universities co-operated in investigating these problems, and as a result much information has been gathered over the years and is collated in this volume.

The first part deals with the medical problems of the amputee—for example, phantom limbs, psychological adjustment, and the principles of prosthetic prescription, but specific instructions regarding the prescription of limbs are omitted. The second part embraces the biomechanics of the upper extremity, the mechanics of voluntary muscle, and the development of prosthetic hands, hooks, cosmetic gloves, and artificial arms. The next section deals with the functional structures of the lower limb—for example, walking and some of the new developments in prostheses. The last section is concerned with the adjustment of the amputee to his limb and some of the problems involved in fitting, alignment, training, and artificial-limb evaluation.

This book has been compiled by 30 contributors headed by Klopsteg and Wilson. Each author has been given a free hand to record his own impressions, but the book is not a textbook, neither is it a guide to how artificial limbs should be made or what is the best type of prosthesis. Much of the information is academic, and in some instances the devices evolved have been found unsatisfactory in practice and have since been discarded. Some of the mechanisms are elaborate and costly to maintain, and in the reviewer's opinion are contrary to the generally accepted principle that a prosthesis should be of the simplest design consistent with effectiveness for its purpose.

There does not appear to be in the U.S.A., as there is in this country, a central organization catering for the whole industry which can develop, reject, or accept mechanisms for artificial limbs. It apparently devolves upon the individual manufacturer to decide what type of device he can best sell rather than what is found by research and long development to be the most suitable for the amputee. The book is, nevertheless, most interesting, and one supposes that for the first time there is included in one volume many different ideas and theories of which the forward-looking prosthetist should be aware.

LEON GILLIS.

## ION EXCHANGE AND ADSORPTION

*Ion Exchange and Adsorption Agents in Medicine.* By Gustav J. Martin, Sc.D. (Pp. 333+vii; illustrated. 63s.) Boston, Toronto: Little, Brown and Co. London: J. and A. Churchill Ltd. 1955.

In the author's foreword, in the material on the dust-sheet, and in the subtitle, "The Concept of Intestinal Bionomics," prominence is given to a theory that "all chronic degenerative disease has as an important component in its aetiology the absorption from the intestine of small quantities of toxic chemicals." The author believes that ion exchange and adsorption materials may be able to prevent this process; but it is admitted that this contention is "as yet unsubstantiated by clinical observations." Fortunately perhaps for the merits of the volume as a whole the development of this theory occupies less than 10% of the book; the argument is oratorical and persuasive but not convincing. The greater part of the book is devoted to an account of the chemistry of ion-exchange resins, and the application of anion exchangers in the treatment of peptic ulcer and of cation exchangers in depleting the body of sodium or potassium. There are also short chapters on adsorption materials other than resins and on chelating agents. It is perhaps unfair to expect from a book of this type a balanced account of clinical indications; but it is surprising to read, for example, that "there seems little question but that the anion exchange resins represent the agent of choice in the treatment of peptic ulcer." The figures in Table 40 (p. 218) do not warrant the conclusion drawn from them on page 219. In Table 1 (p. 10) the ionic composition given for blood is that of plasma or serum.

This book cannot be recommended as a reliable account of the medical applications of exchange resins.

D. A. K. BLACK.

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In *Doctor at Large* (Michael Joseph, 10s. 6d.) Richard Gordon continues the medical saga to which *Doctor in the House* gave such an uproarious start. After qualification the hero finds the outlook intoxicating, and the path to surgical eminence strewn with roses. But even the life of a young doctor turns out to be real and earnest. The post of junior assistant casualty officer at St. Swithin's offered some well-taken opportunities for dropping bricks on the toes of the professor of surgery, and soon Dr. Gordon was knocking at the door of a shady medical employment agency. From then on he gathered experience (not all medical) the hard way. From an industrial practice in the Midlands, where the principal's love-starved wife proved an unusual professional hazard, he moved on to a smart Mayfair outfit, where an electrocardiograph followed the doctor on his rounds in a second Rolls. After a fairly quiet spell in a rural practice, the hero returns to St. Swithin's as temporary senior assistant house-surgeon. In this post he achieves the status of eligible bachelor, and this leads to one of the funniest scenes in the book—dinner with the family of a nurse as a prelude to the announcement of an engagement of which the prospective fiancé was blissfully unaware. In a conversation with Grimsdyke—that admirable man of the world so well portrayed by Kenneth More in the film of *Doctor in the House*—Dr. Gordon reveals the seriousness of his ambitions. Fortunately this has not restrained him from making outrageous, but not unkindly, fun of the medical profession on nearly every page of this book.

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## HYPERPARATHYROIDISM

Endocrine disorders have a habit of masquerading in different guises. The metabolic disturbances which they initiate cause general ill-health, and their effects on individual organs or structures result in local complications which may distract attention from the primary disorder. This is particularly true of parathyroid dysfunction. The hypercalcaemia of primary hyperparathyroidism causes general symptoms of ill-health ; damage to bones and kidneys may cause local symptoms. The relationship between hyperparathyroidism and renal disease is a reciprocal one. Primary hyperparathyroidism leads to renal damage, and hyperparathyroidism may arise secondarily in chronic renal disease. Occasionally the secondary form may follow the primary one in the same patient, so that a vicious circle is established. Drs. S. L. Simpson and R. R. Wilson describe such a case in the opening pages of the *Journal* this week. F. Albright and E. C. Reifenstein[1] have stressed the importance of the renal manifestations, and have pointed out that osteitis fibrosa cystica (the osteitis fibrosa disseminata of von Recklinghausen) is by no means a constant feature of hyperparathyroidism, even in severe cases. In a series of 64 cases at the Massachusetts General Hospital in Boston bone disease was present in only 35 cases, whereas there was evidence of renal damage in 52 cases. Since it is renal damage which most adversely affects the prognosis, it deserves recognition in its early stages.

The characteristic metabolic changes in primary hyperparathyroidism are a raised level of calcium in the serum and a lowered level of phosphate, together with increased excretion of calcium and phosphorus in the urine. The level in the serum of alkaline phosphatase is raised only if new bone is being laid down in response to destruction of bone. Even if there is no obvious bone disease, it now appears to be agreed that the excess calcium in the blood is derived from increased osteoclastic activity resulting from direct stimulation by the parathyroid hormone. This was the view originally put forward by J. B. Collip and his colleagues in 1925.[2] Albright and Reifenstein maintained that the primary action of parathyroid hormone was to increase the renal excretion of phosphate, thus depressing the phosphate level in the serum and reciprocally raising the calcium level. The two opposing views have now been reconciled[1] and it appears that both mechanisms exist, though the direct action on bone is of primary importance in hyperparathyroidism.[3 4]

The increased excretion of calcium necessitates also an increased excretion of water, and polyuria and polydipsia are therefore early symptoms. Hypercalcaemia may give rise to general ill-health, muscular weakness, and gastro-intestinal disorders such as anorexia and constipation, and patients are liable to develop duodenal ulceration. Deafness and aphonia have also been reported.[5] The long-continued excess of calcium in the urine eventually leads to the deposition of calcium phosphate either in the form of renal calculi or as a generalized calcification in the collecting tubules (nephrocalcinosis). Albright and Reifenstein estimate that hyperparathyroidism is present in 5% of all cases of renal calculus in Boston, and there is therefore a good case for estimating the level of calcium in the serum of every patient who has a renal stone.

Early symptoms of skeletal involvement are bone pain and tenderness. General decalcification of the skeleton eventually leads to deformities and pathological fractures. In addition, bone tumours and cysts appear. A bone tumour may be the presenting symptom, as in Simpson and Wilson's case, and biopsy of the tumour may lead to a diagnosis of giant-cell tumour. Tumours and cysts arise most commonly at the ends of the long bones and in the metacarpals and metatarsals. They may also occur in the jaw, so that the patient may first present to a dental surgeon with an epulis. The skull tends to be affected relatively early and shows a characteristic moth-eaten appearance. The teeth are not decalcified, but the lamina dura is invisible round them.

The lesion most often causing primary hyperparathyroidism is a single adenoma of one of the glands. This accounted for about four-fifths of Albright and Reifenstein's cases. Hyperplasia of all four glands or multiple adenomata may occur. Carcinoma is very rare. The adenoma varies greatly in size. It may be smaller than the normal gland, but occasionally it may be large enough to be detected clinically. In as many as 20% of cases it may be present in the mediastinum, owing to the fact that the gland is derived embryologically from the third branchial cleft in close

[1] Albright, F., and Reifenstein, E. C., *The Parathyroid Glands and Metabolic Bone Disease*, 1948, Baltimore.
[2] Collip, J. B., Clark, E. P., and Scott, J. W., *J. biol. Chem.*, 1925, **63**, 439.
[3] Milne, M. D., *Clin. Sci.*, 1951, **10**, 471.
[4] Dent, C. E., *Proc. roy. Soc. Med.*, 1953, **46**, 291.
[5] Simpson, J. A., *British Medical Journal*, 1954, **1**, 494.
[6] Joiner, C. L., and Thorne, M. G., *Guy's Hosp. Rep.*, 1953, **102**, 1.

relation to the thymus gland. Therefore the diagnosis has to be established beyond doubt before asking a surgeon to explore for a tumour, for he may have to make a long search of the neck and mediastinum. The high level of calcium and low level of phosphate in the serum and the abnormally high urinary excretion of calcium, even on a fixed low intake of calcium, are virtually diagnostic, though these changes may sometimes be found in cases of multiple myelomatosis and in cases of metastases in the bones. After removal of the tumour the urinary content of calcium and phosphorus immediately falls, and the level of calcium in the serum falls to normal within 1 to 4 days. When bone disease is present, removal of the whole tumour in one stage is commonly followed by a fall of serum calcium to subnormal levels, not only because the remaining parathyroid tissue is involuted but because calcium tends to pass back from the blood into the bones again. The resulting tetany is apt to be more severe than that which follows damage to the parathyroid glands in the course of thyroidectomy and is much more resistant to treatment. Parenteral administration of calcium salts is required; parathyroid hormone and calciferol or dihydrotachysterol are relatively ineffective. In the course of months or years the bones become recalcified. "Pseudo-bone cysts," containing fibrous tissue, become reorganized and are eventually filled in with bone. True bone cysts (containing fluid) remain permanently.

Secondary hyperparathyroidism arising during chronic renal disease is the result of the failure to excrete phosphate. The retention of phosphate leads to a reciprocal fall in the serum level of calcium, which in turn increases the parathyroid secretion. Osteitis fibrosa rarely develops in these circumstances, but, when it does, it may be indistinguishable from that of primary hyperparathyroidism. When it occurs in children the epiphyses show changes which are radiologically, but not histologically, similar to those of rickets (hence the term "renal rickets"). This is distinct from the condition of osteomalacia which may result from renal acidosis associated with tubular failure without glomerular insufficiency. In the latter case calcium is used as base and the blood calcium level tends to fall; again, this increases the parathyroid secretion, but now phosphorus can be excreted in response to parathyroid hormone and the blood phosphorus tends to be low. The correction of the acidosis with sodium citrate, together with the administration of calciferol and calcium salts to increase absorption of calcium, produces excellent results in cases of pure tubular insufficiency, but in cases of renal osteitis fibrosa may, as C. L. Joiner and M. G. Thorne[6] point out, be ineffective. The importance of Simpson and Wilson's case is that it shows that, once the kidneys are affected in primary hyperparathyroidism, progressive renal damage may give rise to a recrudescence of the hyperparathyroid state even when this has apparently been corrected by surgery, and thus lead to terminal renal failure.

## THE CASE OF THE CHINESE EGGS

During August and September of this year there was a sudden sharp rise in the notifications of enteric fever, mostly paratyphoid fever (see Graph on p. 1338). Since paratyphoid became separately notifiable in 1941 in England and Wales, sudden increases of this kind have occurred, notably in 1948, when there were several simultaneous outbreaks in different parts of the country and all caused by the same phage type (Taunton) of the paratyphoid bacillus. In the days before the Public Health Laboratory Service with its Reference Laboratories was established these outbreaks might have been regarded as unrelated episodes, but the demonstration by the technique of phage-typing, developed for the paratyphoid family by Felix and Callow, that these outbreaks were due to a common infecting type (there are at least 10 different phage types of the paratyphoid B bacillus) was of considerable epidemiological interest.

Most of the outbreaks of paratyphoid fever recorded since the war have been associated with artificial cream added to buns, sponges, éclairs, and the like in which the organism will multiply freely once contact has been made with the flour or other ingredient in the pastries. In outbreaks of typhoid fever it is often possible to trace the source of infection to a chronic typhoid carrier. In paratyphoid, on the other hand, such a connexion is very rarely established, and suspicion has often been directed to symptomless excreters or mild atypical cases as the immediate source of infection. Employees in the bakeries distributing the cream-filled cakes have sometimes been shown to be temporary excreters, but whether these latent cases were responsible for contaminating the cream or were themselves victims of an already contaminated commodity was often in doubt. Indeed, although it has been commonly presumed that the paratyphoid infection has been derived from an unidentified human source, W. C.

[1] Cockburn, W. C., Jameson, J. E., and Fenton, J., *Monthly Bull. Minist. Hlth. (Lond.)*, 1951, **10**, 43.
[2] Thomson, S., ibid., 1953, **12**, 187.
[3] Newell, K. W., ibid., 1955, **14**, 146.

Cockburn and his colleagues[1] in the Eastbourne outbreak of 1950 and Scott Thomson[2] more recently in South Wales have postulated that the infecting organism might have been introduced into the bakery by some contaminated product in common use.

Between August and December, 1954, 51 strains of paratyphoid B phage type 3a var. 2 were identified at the Central Enteric Reference Laboratory. This type had been identified only once in the previous three years, and its sudden appearance warranted close epidemiological inquiry. As a result K. W. Newell[3] was able to record six small outbreaks of paratyphoid, occurring in widely separated districts and associated with cream cakes supplied by six different bakeries. No cases or carriers of the infecting organism were found among the staff of the bakeries, and all the evidence pointed to some common foodstuff as the source of the infection. Suspicion fell on a particular batch of Chinese frozen eggs in tall 22 lb. (10 kg.) containers of an unusual kind, since every bakery used this frozen egg at the material time and in two bakeries this was the only time that the suspected batch was used. In bacteriological examinations of Chinese eggs in three different types of container, 59% of the tall 22 lb. tins yielded salmonellae, 22% of another type of 22 lb. tin were positive, while only 3% of the 44 lb. (20 kg.) containers gave positive results (none of them human pathogens). Unfortunately *Salm. paratyphi B* was not isolated from any of the samples, so that the evidence, although strongly circumstantial, was still incomplete.

The latest instalment in this detective story is told in our present issue by Drs. K. W. Newell, Betty C. Hobbs, and E. J. Gordon Wallace. Two outbreaks of paratyphoid fever occurred in Worthing (14 cases) and in Weymouth (14 cases) in August this year, and the infecting organism was type 3a, which is different from type 3a var. 2 isolated in 1954. The epidemiological evidence pointed to a batch of Chinese frozen eggs in 22 lb. upright tins as the common source of infection. A large sample (152 tins) of this consignment was examined bacteriologically, and this time the infecting paratyphoid B bacillus—type 3a—was isolated, though from only two tins. Two other types of paratyphoid B bacilli were also isolated each from two tins, while *Salm. thompson* was recovered from twenty tins. It is noteworthy that this same salmonella was found in the stools of five of the paratyphoid cases and in three contacts in these two outbreaks.

Chinese egg is not an ingredient of imitation cream, which was apparently the vehicle in these as in earlier outbreaks, and to complete the chain of evidence it is necessary to determine how the cream became contaminated. It is not unusual for the same dispensing vessels, mixing bowls, and the like to be used consecutively as containers for imitation cream and egg mixtures. Inadequate cleansing and sterilization of these utensils could therefore lead to the contamination of the cream, which, incidentally, is usually prepared under good hygienic conditions, and, as issued, contains relatively few bacterial contaminants. The occurrence of infection with type 3a only when two other types of paratyphoid B bacilli were present in the Chinese egg may be related to the uneven distribution of these bacteria in the tins, as was demonstrated by the bacteriological sampling. Perhaps an associated factor is the opportunity for bacterial multiplication in the cream buns, since in paratyphoid fever, in contrast to typhoid, a fairly heavy dose of organisms may be required to initiate clinical infection. It is interesting that, in the outbreaks currently reported, most of the patients bought cakes from retail shops or a visiting van and not directly from the bakery: the greater lapse of time between preparation and consumption would allow more bacterial growth and so increase the risk of infection.

What measures are to be taken to control this menace? Eggs and egg products such as egg albumen are imported in large quantities from many countries. The present trouble seems to be associated with frozen eggs and egg albumen imported from China, and there is evidence that gross contamination with pathogenic organisms is more likely to take place at some factories than at others. A general ban on imports would unnecessarily penalize those exporting companies that maintain good hygienic standards, but obviously there must be a strict bacteriological control on all shipments, as is now being done for egg albumen, carried out before the eggs are distributed to the users. Bakeries and similar food establishments must take scrupulous precautions to prevent contamination of artificial cream and other uncooked commodities from the communal use of unclean utensils that may have been contaminated by potentially dangerous foodstuffs. Besides mixing-machines and dispensing measures, the savoy bag which is commonly used for piping cream and other semi-solid mixtures without being sterilized between times may be a source of danger. And the food-handler should not be forgotten. Despite much propaganda, the standards of personal and environmental hygiene in many kitchens and food factories still leaves much to be desired.

## COLLEGE OF GENERAL PRACTITIONERS

The first annual dinner, the second James Mackenzie lecture, the third annual report, a symposium on obstetrics—all within the space of a few days—are visible signs of the powerful inward purpose of the College of General Practitioners founded but three years ago. A membership of more than three thousand, many of them overseas, is a remarkable achievement at a time when the practising doctor has to think twice before joining still another professional organization or society. The accounts of its current activities published elsewhere in this issue show, indeed, how far the College has travelled since we published the report[1] of its steering committee in 1952.

The *Third Annual Report* is a remarkable document. From this we learn of the success attending on the efforts of the faculty boards, of which there are now twenty-seven. The members of some of these have students in their practices; one faculty has arranged an annual meeting between final year students and general practitioners; another has studied the teaching of certain aspects of general practice to students; the Medical Selection Board of the University of Sheffield has for the past year had among its members a general practitioner nominated by the North Midlands Faculty Board; other boards have arranged postgraduate courses of one sort and another; and the research committees have been fruitfully active. Nine faculties have been established overseas.

The College has persistently urged that general practitioners should join in the teaching of medical students,[2] and this is the theme of the second James Mackenzie Lecture, by Dr. G. O. Barber, reported at p. 1323. Dr. Barber agrees with those who consider that the aim of medical education is to produce "a good basic doctor," but insists that the student must receive a much broader view of disease than can be obtained within the four walls of a hospital. And he argues that students need some preparation for the greatly altered conditions of practice when they leave hospital after qualification. It has been suggested before in these columns that this preparation might be made in the second half of the compulsory pre-registration year, when the graduate is likely to have made up his mind whether or not to enter general practice. Learning by doing must be the final process of education of any doctor whether in general or in special practice. Dr. Barber's dictum that he "would rather be in the hands of a man with an accurate knowledge of medicine . . . than in the care of the kindest man imaginable who did not really know his job" will command general agreement. And the foundation of this accurate knowledge must be laid in the academic but vocational period of study in the teaching hospital. This is not to say that the curriculum is all it should be, and the First World Conference on Medical Education—the theme being undergraduate education—produced enough ideas by which medical educators can take stock of their position in the years to come. The suggestion that the College of General Practitioners has made to the General Medical Council, that an observer from general practice should be appointed to each medical school, would seem to be unexceptionable. With this as a first step, it should subsequently be seen whether it is practicable, or even desirable, that departments of general practice should be established in medical schools. All those concerned with medical education will note with interest the report of the examination committee of the College, and its conclusion that an examination for the postgraduate diploma of membership of the College of General Practitioners is practicable and should consist of written, clinical, and oral examinations; and the Annual Report contains thirteen pages which give in some detail a provisional basis for a syllabus. The College has not yet come down on the side of holding such an examination, and those who think there is already a surfeit of diplomas may hope that the College will avoid adding one more to the list. Perhaps the most encouraging of the College's activities is its research organization, for there can be little question that general practice offers unrivalled opportunities for research into clinical medicine, opportunities often perforce neglected because of lack of time and perhaps by lack of stimulus. This stimulus the College is providing.

Since 1948 many reports on general practice have appeared, predominantly analytical and in places highly critical. It may be unfair to set against these the quite different annual reports of the College of General Practitioners. But these reports are the most encouraging documents that have been published for many a day. They are packed full of constructive ideas and of records of good work done by good men. Here we seem to see a veritable renaissance of general practice which has behind it men of vision, energy, and courage who, like the men who founded quite a different kind of society in the seventeenth century, eschew politics and seek to add to knowledge as well as take part in its organization.

[1] See "A College of General Practitioners." Report of the General Practice Steering Committee (1952). *British Medical Journal*, 1952, **2**, 1321.
[2] See "Report on the Teaching of General Practice by General Practitioners," *British Medical Journal*, 1953, **2**, 36.

## BRONCHITIS AND CANCER

It has often been noted that long-standing bronchitis is a common complaint of patients with lung cancer, but bronchitis is a common disease, and in the absence of precise knowledge of the incidence of bronchitis in the general population it has been impossible to say whether the two diseases occur together more often than would be expected by chance. The evidence now produced by R. A. M. Case and A. J. Lea[1] shows that they do. By means of data provided by the Ministry of Pensions they have been able to show that there have been approximately twice as many deaths certified as due to lung cancer among 1,421 pensioners of the first world war, who were recorded as having bronchitis at the time they were pensioned, as would have been expected among a similar group of men in the general population of England and Wales (29 lung cancer deaths against 14 expected). In contrast, the number of deaths certified due to cancer of other sites and the expected number of such deaths were almost equal (75 and 81). Serving soldiers who had been pensioned for the loss of a leg showed no excess mortality from lung cancer—there were 13 such deaths among a group of 1,114 soldiers, while 16 were expected—so that it is likely that the excess among the bronchitics was related to their medical condition rather than to any special attribute of Service life.

Case and Lea point out that in an investigation of this type several sources of bias may have contributed to the result. The cause of death, as certified to the Registrar-General, is not always accurate, and a chronic history of chest disease may well have influenced the doctor who certified the death in his choice of diagnosis. Possibly a pre-existing chest disease would cause a more careful examination of the respiratory system and a consequent discovery of cases of malignant disease which would otherwise be missed; or lung cancer might be positively and incorrectly diagnosed through misinterpretation of symptoms and signs due to the underlying chronic condition. On the other hand, a chronic chest lesion might lead to a diminished tendency to diagnose lung cancer, because of a distaste for diagnosing two diseases together. The first two reasons for bias might, perhaps, account for the observed result; the last would mean that the real difference was underestimated. It is a matter of opinion which is the most likely, but in the present state of knowledge the authors' opinion that lung cancer is more likely to have been under- than over-diagnosed would seem to be the most reasonable.

The result may perhaps be explained if bronchitis, like lung cancer, is in part caused by long-continued smoking. According to K. N. V. Palmer[2] bronchitis is commoner among smokers than among non-smokers, and the incidence of the disease increases with the amount smoked; but the evidence adduced is not conclusive. Alternatively, it may be that the inflammation and degeneration associated with the disease directly predispose to cancer. Such a hypothesis accords well with the observations of C. Raeburn and H. Spencer,[3] who found as many as nine microscopic "cancers" in association with scars in the periphery of the lung and one small unsuspected carcinoma in a large bronchus in 750 necropsies.

It is of some interest that Case and Lea had not intended their work to be a study of bronchitis; their object was to find out if mustard gas, which is known to be carcinogenic to animals, was carcinogenic to man in the doses to which soldiers had been exposed in the first world war. In fact they found that men who had been pensioned for the effects of mustard gas suffered a mortality from lung cancer and from cancer of other sites almost exactly the same as that suffered by men pensioned for bronchitis who had never been exposed to mustard gas. Since there was clear evidence of bronchitis in nearly all the mustard-gas pensioners, the conclusion was inescapable that it was the development of bronchitis rather than exposure to the gas which was associated with the increased risk of lung cancer.

The study is the first to have been reported in which the basic data have been drawn from the records of the Ministry of Pensions. The enterprise of the Ministry in co-operating with medical research workers is to be welcomed; it has already led to an important addition to knowledge, and it may be expected to produce many more in the future.

[1] Case, R. A. M., and Lea, A. J., *Brit. J. prev. soc. Med.*, 1955, **9**, 62.
[2] Palmer, K. N. V., *British Medical Journal*, 1954, **1**, 1473.
[3] Raeburn, C., and Spencer, H., *Thorax*, 1953, **8**, 1.

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## INHERITANCE OF DIABETES INSIPIDUS

Diabetes insipidus may be due to a variety of lesions, traumatic and neoplastic, interrupting the connexions between the supraoptic nuclei and the posterior lobe of the pituitary. In many cases, however, no cause can be found. It has also been known for more than a century that in some families the condition appears to be inborn. Two extensive pedigrees showing straightforward dominant inheritance were published at the end of the last century,[1 2] and these families have been brought up to date.[3 4] A similar American family has recently been reported.[5] In this family the great-great-grandmother of the index case was in the habit of going to the creek in the middle of the night to get a bucket of water to drink, while six generations later one of the granddaughters of the index case, aged only 20 months, was already drinking almost continuously, her earliest speech being "wa-wa."

But it was early noted[6] that there was a definite excess of males among patients with diabetes insipidus, and pedigrees have been published[7] which in retrospect are seen to suggest sex-linked inheritance. It was not, however, until Forssman's thorough study[8] in Sweden in 1945 that sex-linked inheritance of diabetes insipidus was clearly recognized. From the genetic viewpoint, therefore, at least two distinct genes may cause diabetes insipidus.

[1] Weil, A., *Arch. path. Anat.*, 1884, **95**, 70.
[2] Lauritzen, M., *Hospitalstidende*, 1893, series 4, pp. 1, 2, 358, 392, 423, 451.
[3] Dölle, W., *Z. menschl. Vererb.- u. KonstitLehre*, 1951, **30**, 372.
[4] Ellermann, M., *Acta psychiat. scand.*, 1939, **14**, 233.
[5] Levinger, E. L., and Escamilla, R. F., *J. clin. Endocr.*, 1955, **15**, 547.
[6] Weil, A., *Dtsch. Arch. klin. Med.*, 1908, **93**, 180.
[7] McIlraith, C. H., *Lancet*, 1892, **2**, 767.
[8] Forssman, H., *Acta med. scand.*, 1945, suppl. 159.
[9] Waring, A. J., Kajdi, L., and Tappan, V., *Amer. J. Dis. Child.*, 1945, **69**, 333.
[10] Williams, R. H., and Henry, C., *Ann. intern. Med.*, 1947, **27**, 84.
[11] Forssman, H., *Amer. J. hum. Genet.*, 1955, **7**, 21.

Classification by response to antidiuretic hormone of the posterior lobe of the pituitary was found to cut across the genetic divisions. Patients in the families with the dominant pattern of inheritance and also those in some of the sex-linked families showed an excellent response to the antidiuretic hormone, but patients in other families were refractory to this hormone,[8 9] and R. H. Williams and C. Henry,[10] describing one such family, coined the term "nephrogenic" diabetes insipidus for this type. H. Forssman[11] has recently brought his sex-linked families up to date. In one enormous pedigree, including hundreds of individuals and eight generations, the type is pitressin-sensitive. Some of the carrier women suffered from diabetes insipidus in the last few months of pregnancy, but became free of the disorder a few days after delivery. This phenomenon also occurs in the dominant forms. Other carriers showed no symptoms at all. Another family is of the same type. But in a third family covering four generations the condition is refractory to pitressin. The nephrogenic form would appear to be clinically the more severe. In consequence the mutant genes will persist on the average for fewer generations. This clinical differentiation by response to pitressin makes it clear that at least two distinct sex-linked genes may cause diabetes insipidus, which with the dominant gene make three in all.

## HYPNOSIS AND BURNS

The badly burned patient has a moment of acute fear, followed by three to six months in hospital—but stone walls alone do not make his prison. He is suddenly faced with a threat to survival, the fear of disability and disfigurement, prolonged discomfort, and an unknown number of dressings and operations. Moreover, he may be overwhelmed with feelings of guilt that the accident was caused by his own negligence, loss of purpose due to shattered ambitions, and loneliness if separated from his family or afraid of rejection by one he loves. It is little wonder that some fail to adjust themselves to their new environment and become loud and demanding or sullen and uncommunicative. The scant attention given to the psychosomatic aspect of the treatment of burns is not surprising. The chief priorities for saving life are resuscitation, the control of infection, early grafting, and adequate nutrition, and the spread of facilities for these vital emergency measures is all-important. Only now are they becoming available with the establishment of burns units in various parts of the country, and an attempt to add expert psychotherapy at the present time might well delay the provision of these essentials.

The emotional problems of burned patients, however, have been carefully studied by Cobb and Lindemann[1] after the Cocoanut Grove fire in Boston in 1943, and by Hamburg and his co-workers[2] in a further 400 cases in 1953. More recently the use of hypnosis has been investigated by Crasilneck and his colleagues[3] at Dallas, Texas. They claim that hypnotic and post-hypnotic suggestion can sometimes be used as an anaesthetic and analgesic agent, that it can stimulate tremendous appetites in persons otherwise not inclined to eat, and that it has been successful in correcting some of the patient's detrimental emotional responses and failure to accept the situation realistically. Two of their eight patients, however, were not amenable to hypnosis, and the high proportion of young children and aged usually found among the extensively burned suggests that hypnotic suggestion would be of occasional value only. The changes produced in appetite are the most striking feature of the study by Crasilneck and his colleagues. Adequate nutrition can usually be maintained in burned patients without much difficulty by continuous feeding through an indwelling naso-gastric tube, but some patients find this a real hardship. The creation of an artificial appetite, raising the patient's voluntary intake from 2,000 to 8,000 calories a day during a fortnight's hypnosis, is a dramatic result which might well be life-saving—especially when it includes a selective desire for the right foods and is obtained without discomfort.

Recovery from an extensive burn is a marathon race which tests the staying power of every patient. His good progress is usually proportional to the care spent upon him, and it would certainly be a step forward if he could be saved the discomfort of some of the present therapeutic techniques. It is at least encouraging that the method of hypnosis is going to be investigated further by the Dallas workers.

[1] *Ann. Surg.*, 1943, **117** 814.
[2] *New Engl. J. Med.*, 1953, **248**, 355.
[3] *J. Amer. med. Ass.*, 1955, **158**, 103.

## HEROIN

The space and prominence given in *The Times* to the banning of heroin adds powerful support to those who for many reasons are disquieted by this action of the Government. The British Medical Association has made its objection to the ban in unequivocal terms, and few actions can have spoken louder than words than the action of many hospitals in accumulating stocks for the relief of their patients' suffering. All drugs are open to abuse, and recent reports have, for example, drawn attention to the growing addiction to pethidine, one of the remedies previously advocated as an alternative to heroin. But it may be doubted whether a ban on the manufacture of heroin will control addiction. In a letter to *The Times* in May this year Dr. Kenneth Harris, Mr. D. R. Laurence, and Professor M. L. Rosenheim pointed out that the manufacture of heroin from opium or crude morphine is a simple matter. Prohibition of legitimate manufacture may therefore have little if any effect in the control of addiction; like other forms of prohibition it may even stimulate addiction and increase the price of the article. As Dr. Harris and his colleagues said: "If the prohibition assisted in the world-wide control of heroin addiction it would, we feel sure, be welcomed by the profession." As it seems improbable that it would have this effect, and as many highly experienced medical men consider heroin to be a drug which cannot be satisfactorily replaced by others, it is to be hoped that the Government will see the wisdom of having second thoughts on the subject.

# *EMERGENCIES IN GENERAL PRACTICE*

# ACUTE PSYCHOSIS

BY

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Acute psychoses are not rare conditions. Statistics for admission to mental hospitals and observation wards indicate that the family doctor will be fortunate if he is not called on to deal with many such emergencies during his career. Few practitioners relish the responsibility of the acute mental case, for it can be among the most difficult of emergencies with which he is called upon to deal. There exists, of course, for the disposal of such cases a lay official known as the duly authorized officer (D.A.O.), who, as the law stands at present, has the authority and means to place the acute mental patient into a suitable hospital without the intervention of a doctor. In practice the D.A.O. will be found only too willing to accept the help and medical backing of the general practitioner; for the latter to deflect the whole responsibility on to a layman is never in the best interests of his patient.

When a doctor is called to see an acutely psychotic case he has to make several decisions of great consequence to the patient. The summons, "Please come at once; Mr. Jones has run amok," is not the only way in which an acute psychosis may come to the notice of the practitioner. Though violence, destruction, and general bedlam are the most striking manifestations, acute psychosis can, and often does, present in a far less dramatic way. Relatives can easily see the need to take action with the grossly excited, but it often needs medical skill and experience to recognize under the disguise of quarrelsomeness, peevishness, or physical complaints the acutely suicidal melancholic who is equally an emergency in general practice. Facile cheerfulness and jocularity may disguise a hebephrenic schizophrenia; egotism, callousness, and brutality towards the nearest and dearest may be the first indication of a senile psychosis.

Acute psychosis is not a disease entity but a global term applied to a group of grossly pathological disorders of behaviour and mental state. It is a medical equivalent of "insanity," which is a legal term implying that the patient is unable to care for himself or constitutes a danger to himself or others. The psychoses are distinguished in broad terms from less serious mental aberrations by the presence of one or more of the following criteria: loss of contact with, or marked distortion of, reality; severe and persistent disturbance of emotional expression; gross deviation from normal, socially accepted behaviour; sudden disintegration of the patient's former personality; rapid deterioration of the previous level of intellect and common sense.

### Investigation of the Patient

Correct diagnosis is of paramount importance in medicine, and the acute psychoses are no exception. To reach the conclusion that the patient is of unsound mind is enough for the magistrate involved in certification, but the doctor must go further. In the diagnosis of the acute psychotic states, the history, with few exceptions, is far more important than examination of the patient. Often prodromal symptoms of a psychotic breakdown have been present for some time, and so the doctor will have been prepared for it; alternatively he may be surprised by its appearance without warning in a patient whom he already knows well. If the case is new to him he should take the history from a relative or friend before the patient is seen; many acute psychotics are unable or unwilling to give a coherent account of themselves. The patient can then be seen with a clear knowledge of what to expect.

It is a good rule never to interview the relatives in the presence of the patient and to interview only one informant at a time. The members of the patient's family are not infrequently in a highly emotional state, and if seen all together they are more likely to confuse than to clarify the story by their interjections and interruptions. Spare relatives can be dispatched to watch the patient; for it is not unknown for the latter to run away or to attempt suicide on the arrival of the doctor. Under no circumstances should the patient be left alone. If it is impracticable to interview the relatives in the house or that of a neighbour, it is a good plan to take the history while sitting in the car with the informant in the front seat and the doctor at the back so that he is not embarrassed by having his notes read. It is sometimes possible to obtain a fairly full history over the telephone when first called, or in less urgent cases to persuade a relative to call at the surgery before the doctor visits the patient.

Once adequate information on the past history and development of the symptoms has been obtained, the doctor should proceed to interview and examine the patient. Prudence and common sense dictate that a doctor should not go by himself to examine a possibly dangerous patient. The history will brief the doctor on how much assistance will be required, and this should always be mobilized beforehand. It is often surprising how an acutely excited patient will quieten down and submit to examination when he sees that strength is not on his side. If when the doctor sees the patient he is properly briefed by the history and is accompanied by adequate helpers he has little to fear.

The speech and manner in which the doctor approaches the acute psychotic patient will do much to help his examination. Patients who are apparently quite out of touch with their surrounding may nevertheless be aware of how they are approached. The patient will certainly remain quite inaccessible if talked down to as if he was a child. A hectoring approach may arouse fury and resentment, while a timid and fearful manner may provoke a like response. Generally the acute psychotic should be talked to in the same friendly manner as if he were sane. It is uncommon for these patients to lie to simple straightforward questions, and it is unwise for the doctor to try to trick his patient into admitting delusions and hallucinations. It is equally important to listen well as to question well. If the doctor does most of the talking he will learn little of the patient. During the interview much can be learned from the patient's appearance, gestures, and general behaviour, as well as from what he says and how he says it. Physical examination should be carried out wherever possible, but this is not always practicable in the acutely resistive patient. In a surprising number (around 10%) of acute psychotics admitted to observation wards the mental symptoms are secondary to underlying physical conditions.

### Differential Diagnosis: The Symptomatic Psychoses

Possibilities to bear in mind during physical examination are the acute toxic psychoses that follow the administration of drugs. Dilated pupils and a dry mouth suggest the possibility of an acute belladonna psychosis. Similar reactions may follow the use of other drugs such as bromides, amphetamine, cortisone, and some industrial poisons. The history of recent medication should clarify the matter. Other organic conditions which are not as rare as might be expected are the acute psychoses occurring in epilepsy, such as twilight states and other psychomotor symptoms; in myxoedema; in the vitamin-B deficiencies, with acute infections (pyrexia gives the lead here); and following operations and childbirth. Though rarely seen nowadays, G.P.I. can present as a dangerous excitement or as just the opposite. Acute alcoholic psychoses may be suspected from an array of empty bottles, and may be combined with other abnormalities such as head injury, epilepsy, etc. Roughly speaking, the acute psychoses which are symptomatic of some underlying physical disease should be thought of when there is clouding of consciousness, restlessness, visual hallucinations, and paranoid ideas which fluctuate during the day and night.

Excluding the acute symptomatic psychoses, one is left in broad terms with the differentiation of acute schizophrenic psychoses from affective conditions (manic and depressive), from psychotic reactions in epilepsy or in arteriosclerotic and senile illness, and from psychosis-like outbursts in hysterical and psychopathic personalities. The following pointers, though oversimplified, may be helpful in the recognition of these conditions. The differentiation depends almost entirely on the clinical picture and history as a whole, and very rarely on single or groups of symptoms.

### Hysteria and the Affective Psychoses

Hysterical outbursts may occur in relatively normal persons under exceptional stress—for example, loss by sudden death of a close relative or an accumulation of unlucky events. If they happen after minor mishaps, it is usually in patients of obviously hysterical or psychopathic personality; there is invariably a history of instability and maladjustment dating back to childhood or adolescence. There is also often a history of similar episodes, so that the relatives are not taken by surprise at the outburst. The hysterical explosion is tinged with melodrama, threats, and over-demonstrativeness. The more reactive the audience the greater the show. It is well to remember that such hysterical outbursts may mask an underlying physical disorder such as cerebral tumour or encephalitis which if undetected will become a monument in the doctor's practice. Both psychopath and hysteric remain clearly in touch with their audience.*

The affective psychoses (manic-depressive psychosis and involutional melancholia) are characterized by a pronounced and persistent change of mood. These patients may have shown marked mood swings for years before the acute breakdown, but are otherwise stable individuals. A gradual onset is commonest, though the doctor is often not called until an acute exacerbation of symptoms sets in. The depressive psychoses are characterized by a marked melancholy of mood, slowing of responsiveness, self-reproach, feelings of guilt, delusions of persecution, and agitation. There are often suicidal tendencies, insomnia, anorexia, and preoccupation with bodily function. Suicidal ideas in these cases must be taken seriously. In the manic psychoses there are excitement, elation, hyperactivity, and an uninhibited flow of talk. Such patients are often irritable, laughing and crying at the same moment, and readily distracted from what they are doing by any chance stimulation. Rarely, acute mania and depression present as stuporous states with the patient mute, inaccessible, and refusing to eat. Unlike the symptomatic psychoses, the affective psychoses occur in a setting of clear consciousness.

*See also Dr. Gerald Garmany's article in this series, "Acute Anxiety and Hysteria" (July 9, p. 115).

### Acute Schizophrenia and Other Psychotic Reactions

The differentiation of the affective psychoses from acute schizophrenia may be difficult, but, broadly speaking, the behaviour of the manic or depressed patient is related to his prevalent mood. The behaviour of the schizophrenic is, on the other hand, often incongruous to his mood, which vacillates irregularly and lacks the expressive quality of the affective states. Schizophrenics show a wide variety of bizarre forms of behaviour and mannerisms. The inability of the examining doctor to feel with his patient and to understand his train of thought, even though it sounds superficially plausible, is highly characteristic. A state of immobility lasting for minutes or hours, and perhaps interrupted by unexplained overactivity when disturbed, may be an early sign of catatonic schizophrenia. The history of a patient with acute schizophrenia often discloses prodromal symptoms of gradual social withdrawal, falling off of activity and interest, and increasing remoteness.

Epileptic furor and twilight states may closely mimic certain schizophrenic states. There is, however, a history of fits and clouding of consciousness. Mental defectives are prone to psychotic episodes which clear up, leaving the patient in his previous state. Here the history of backwardness should clinch the diagnosis. It is not unknown for patients who are expecting legal prosecution to feign psychotic behaviour, but in these cases the picture is only a replica of the patient's idea of madness, and the well instructed is rarely misled to diagnose psychosis.

An acute psychotic episode may be the first indication of senile dementia. These patients are restless, often delirious, and invariably disorientated. They cannot answer questions on their whereabouts, the time of day, and the date. With an ageing population these cases are becoming increasingly frequent.

### Management

Acute psychotics are often dangerous to themselves and others, so certain precautions should be taken. It is better to take too many precautions than too few. If the patient rejects tactful handling and persuasion, which should always be tried first, force must be used in his own interests. The mere presence of three or four other persons may make any physical coercion unnecessary. If dangerous and armed, the help of the D.A.O. and police should be sought immediately, but no more force than is necessary to restrain the patient should be used. It is not unknown for relatives to relish the chance of getting their own back on an overpowered patient who in earlier episodes of his illness may have been an annoyance. Psychotic patients, particularly catatonics, react with great sensitivity to their environment. They are often relatively quiet until interfered with. It is therefore wise to avoid all unnecessary interference and to reserve force for the moment of real necessity—for example, when giving an injection or removing the patient to the ambulance.

Constant vigilance is the only sure way of preventing suicide. The patient should be kept on the ground floor to prevent jumping from a height. He should be undressed, shoes being removed first, and, if delay in removal to hospital is unavoidable, placed on a mattress on the floor, and kept warm between blankets. Sharp objects, penknives, scissors, etc., should be removed, together with belts, pyjama cords, and medicine bottles, which might be used for suicidal attempts. The patient should be accompanied to the lavatory. If he will take fluids, they should be given liberally to avoid dehydration.

Adequate sedation is essential. For patients who can swallow their medicine, 6 gr. (0.33 g.) of sodium amylobarbitone may be given by mouth, but it often proves

ineffective in an excited patient. Paraldehyde up to 3 dr. (11 ml.) is reliable and acts quickly, but its taste is repulsive. If intravenous injection is possible, 5–10 ml. of a 10% solution of hexobarbitone sodium, injected slowly, 1 ml. a minute, will serve the purpose. Most cases of this kind, being restless, obstructive, and uncooperative, require sedation by hypodermic injection. The most useful and well-tried combination for the uncontrollable patient is 2 ml. of morphine and hyoscine injection (*N.F.*), which contains ¼ gr. (22 mg.) of morphine and 1/75 gr. (0.86 mg.) of hyoscine. If this is not effective, one-half of this amount can again be injected one hour later. Although the morphine multiplies the sedating effect of hyoscine in this combination, it should be remembered that morphine in itself is not a sedative and has almost no calming effect on the psychotic patient, but may lead after admission to hospital to retention of urine often difficult to overcome.

A relatively harmless but very helpful measure is two injections of paraldehyde injection (*N.F.*), 5 ml. deeply into each buttock. This can also be repeated in hourly intervals until adequate sedation is achieved. The stoutest needle available should be used.

## Disposal

Treatment of the acute psychotic patient in the home is generally impracticable, and it is therefore in the best interests of all concerned to have the patient removed to an observation ward in a general or a mental hospital. Having excluded transient mental upsets, such as occur in drunkenness or psychopathic reactions—for example, in hysterical states—which are likely to settle rapidly at home with some mild sedation, the doctor is faced with the problem of how admission can be best arranged.

What is done depends largely on whether the patient is willing or unwilling to enter hospital. Nowadays a high proportion of acute psychotics are admitted and treated as voluntary patients, and, if this is at all possible, it is certainly in the patient's best interests. If the patient agrees to voluntary treatment, the doctor should telephone the duty medical officer of the hospital in the district where the patient resides to see if a bed is available. Hospital catchment areas vary considerably in different regions. Precise information on local arrangements can be obtained from the D.A.O., whose telephone number is usually under the borough or county health department. Some patients, having consented to enter hospital voluntarily at first, change their mind when they reach hospital and refuse to sign the voluntary form. This is a risk that has to be accepted.

When dealing with the unwilling patient the procedure differs according to whether the relatives wish for treatment under the National Health Service or whether they are willing and able to pay the fees for a private hospital. In the former case the procedure is easy and consists in telephoning the D.A.O. and informing him of the position. The doctor will be well advised to leave the legal side of the admission to the D.A.O. He should remember that the precise procedure to secure admission rests with this officer, who is legally responsible and can act at his own discretion. D.A.O.s are usually co-operative and helpful, and, as mentioned before, they like to have their decisions backed by the general practitioner. In the case of a "Three-Day Order" they like a note (not required by law) saying, in effect, that the patient is in urgent need of observation to determine his soundness of mind.

The best and most convenient procedure for the non-voluntary private patient is by an Urgency Order, which is not identical with certification. It lasts for seven days, allowing sufficient time for further appropriate action to be taken. Having ascertained if the selected hospital can take a private patient, the nearest relative available signs as petitioner and the doctor completes one medical certificate stating the reasons for the patient's urgent admission. A magistrate is not required. The relative who signs must have seen the patient within two days and must complete a statement of particulars. Urgency Order forms are self-explanatory and can be obtained from a law stationer.

If the doctor acts with good faith he has little to fear about later legal repercussions; in case of doubt about any legal point concerning the admission of the unwilling patient, the D.A.O. is a good source of information. In Scotland the emergency, whether in a private or National Health Service patient, can be dealt with simply by a Certificate of Emergency (one medical certificate and a petition), which allows the patient to be retained in hospital for three days.

The procedures mentioned, though not the only ways, are the most convenient and frequently used for getting cases of acute psychosis into hospital. Once in the hospital the psychiatrist will take responsibility for arranging further treatment as a temporary, certified, or voluntary patient.

## Dealing with the Relatives

In dealing with a case of acute psychosis the doctor has to cope not only with the patient but with his relatives and friends, who are often nearly as distraught as the patient himself. Many of the difficulties in dealing with these cases are created by the relatives, who envelop the house with an atmosphere of alarm and mystery. By adopting a quietly confident manner and getting all to regard the patient as somebody who is sick and needs treatment, he can do much to dispel their unfounded fears and dreads. He should resist attempts by anxious relatives to introduce himself to the patient as the "insurance man" who has just dropped in, or by some similar subterfuge. The doctor should always tell the patient who he is and why he has come.

Relatives prefer to be told that the patient is mentally ill rather than insane, and welcome a plainly reasoned statement of the action needed in the patient's best interests. Undue pressure from relatives to have a mildly confused senile patient put away should be resisted, particularly if there is reason to suppose that the condition is only transitory, accompanying an infection. Conversely the need for hospitalization of the acutely suicidal depressive should be stressed to reluctant relatives. The interests of the patient always take precedence over those of his relatives. Sometimes the relatives of these patients prove to be particularly difficult, in which case a firm but tactful attitude is essential. As a last resort one can point out that it is the doctor's duty to inform the D.A.O. of the emergency and of the relatives' refusal to abide by medical advice. In borderline cases a domiciliary visit by a psychiatric consultant may be a way out.

The relatives often ask for a prognosis, but in only a few cases will even the specialist have sufficient information to predict the likely outcome after one interview. The best line is to explain that with recent advances in treatment the outlook is much more hopeful than is commonly supposed, and that only by full investigation in hospital can a definite prognosis be made. It is unwise to hazard a guess about the kind of treatment that will be given in hospital. Not infrequently difficulties arise when relatives have been told by the family doctor that some special therapy will be applied, and they find out from the specialist that it is not indicated. It is unfortunate that once in hospital the family doctor all too often loses sight of the patient until his discharge. Acute psychotics do often recover, and on leaving hospital need the support and encouragement of their own doctor during convalescence.

The worst mistakes arise from failure to recognize the acutely suicidal depressive, or when the doctor takes only one anxious peep round the front door and without further ado arranges for admission to hospital.

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**Next article on Emergencies in General Practice:—** "Haemorrhage in the Newborn," by Professor Wilfrid Gaisford.

# COLLEGE OF GENERAL PRACTITIONERS

## JAMES MACKENZIE LECTURE

Dr. G. O. BARBER, chairman of the Undergraduate Education Committee of the College of General Practitioners, delivered the second James Mackenzie Lecture in the Great Hall of B.M.A. House on November 19. His subject was the education of the medical student.

### Aims of Medical Education

The branch of medicine in which a man would eventually practise should not be taken too much into account, said Dr. Barber. What was wanted was to turn out "a good basic doctor." He should have professional skill, a humane outlook, and some organizing ability, in that order of importance. "There may be some of you who would question my putting professional skill before humanitarianism. But," Dr. Barber continued, "I am of the firm opinion that I would rather be in the hands of a man with an accurate knowledge of medicine . . . than in the care of the kindest man imaginable who didn't really know his job." It followed that the student—whether he was to be general practitioner or consultant—must be taught the various branches of medicine by the specialists. But—and it was a big but—he must be given a much broader view of disease than was possible in hospital alone. The most important service a doctor could render his patients was to recognize illness at its earliest possible stage, and it was those early stages of disease that were so conspicuously absent from student teaching material. Disease was something which started outside the hospital, and to get a true perspective the student *must* have opportunity to study the whole picture and not just a slice of it.

Academic skill without humanitarianism was barren. St. Paul's "charity"—ἀγάπη—or sympathy was also necessary. It could be defined as the sum of all those qualities, apart from professional skill, that one looked for when selecting a doctor for one's own family. Lastly, a doctor needed organizing ability if he was to use his professional powers to the best advantage, but this was best come by after qualification. The general practitioner stood or fell by his own initiative, and students needed some preparation for the great changes in the conditions of practice they would find outside hospital.

### Training of the Student

How could the profession contribute to the education of the next generation of doctors? First, by taking this responsibility seriously. Surely every practitioner had something to hand on. Those who took clinical students into their practices—and more and more practitioners were needed for this—must have a very clear idea of what they were trying to demonstrate. There was the need to drive home the importance of the apparently trivial complaint which might be the start of serious disease. Secondly, the truth that everyone's health fluctuates throughout life, each body reacting in its own individual manner to stress. A vast amount of work in general practice concerned the chronic patient, whose infirmities could be only alleviated, not cured. These cases were the highest test of good general practice. Two other things the student needed to be shown: the real, but often concealed, influence of the mind on bodily health, and the importance of maintaining contact with patients sent to hospital and with those in charge of them. Lastly, practitioners should let students know that general practice could give, as Dr. Barber put it, "that satisfaction in one's work which ranks only with a happy married life in the good things we can find in this world."

Dr. Barber then addressed himself for a moment, and with respect, to those who teach in hospitals. Were they satisfied, he asked, that they knew the problems of general practice well enough for their academic teaching to be applied in cramped consulting-rooms and slum bedrooms? Did they always remember how closely their students observed and were influenced by their handling of patients? Students wanted a measure of dogmatism in their teaching. They liked the man who was sure of himself and who did not require every negative laboratory finding before reaching a diagnosis. Much waste of *x*-ray film and laboratory time was due to teaching excessive caution.

### The Curriculum

What could be said constructively about the medical curriculum? Dr. Barber confessed he was whole-heartedly in favour of examinations, but attention should be paid to how a candidate set about a question rather than to his knowledge of abstruse fact. So far as the content of the curriculum was concerned, he agreed with Professor Alexander Muir, writing in the educational number of the *British Medical Journal*,* about the disproportion between teaching time for, and experience later in practice of, such subjects as minor psychiatric disturbances, skin complaints, and E.N.T. conditions.

Although he himself had been brought up with the idea that the more abstruse the matter and abstract the subject the better could a logical habit of mind be instilled, he felt nowadays there was so much knowledge to be imparted that mental discipline should be learnt on subjects which themselves would be helpful later. The preclinical subjects needed drastic pruning; function and structure should be taught at the same time and preferably by the same person. Pure anatomy could be reserved for the Fellowship candidate. Gone also were the days when every doctor was expected to be able to perform any operation in the textbook of surgery. In the clinical period there was need for greater familiarity with general practice on the part of teaching consultants, and for a greater integration of the various branches of medicine. It would be instructive, for instance, if surgeons regularly did a round in the medical wards and *vice versa*. The psychiatrist, and particularly the general practitioner, could with advantage play a greater part in the teaching on general medical and surgical cases. "If a senior general practitioner were given a recognized position in a medical school," said Dr. Barber in conclusion, "he could see that all students are given a first-hand insight into general practice as part of their basic training."

## THIRD ANNUAL GENERAL MEETING

In the Great Hall at B.M.A. House on November 19—the anniversary of the foundation of the College—the third annual general meeting of the College of General Practitioners took place with a large attendance of members and associates and with the president, Dr. WILLIAM PICKLES, presiding.

### The Year's Progress

In presenting the annual report (see below) Dr. GEORGE ABERCROMBIE, chairman of council, congratulated Dr. Pickles on having been admitted to the honorary fellowship of the Royal College of Physicians of Edinburgh and on being the first recipient of that college's James Mackenzie Medal (see this *Journal*, November 12, p. 1218). He also congratulated Dr. C. A. H. Watts, who delivered the John Matheson Shaw Lecture to the Royal College of Physicians of Edinburgh on November 11.

Four new overseas faculties had been formed, continued Dr. Abercrombie—in Eire (Cork), in Western Australia (Perth), and in New Zealand (Christchurch and Dunedin), and an Australian Council of the College was being planned. The *Research Newsletter*, under the editorship of Dr. R. M. S. McConaghey, had been greatly enlarged. It was now printed and sent quarterly to every member and associate.

The examination committee had published its report. It had shown that if, at any time in the future, an examination were considered advisable as a method of entry to membership of the College it could be held. Any proposal, however, would have to be passed as a special resolution (of which due notice would be given) by a majority of not less than three-fourths of the votes cast at a general meeting of the College. The question whether or not an examination would be required remained for earnest and thoughtful

*August 27, 1955, p. 526.

consideration. When referring to the reports from the 27 faculties Dr. Abercrombie said that no one could read those pages without a sense of pride and satisfaction that so much had been accomplished by the faculties in so short a time. It had all been done by the initiative of faculty boards in requesting and securing the co-operation of university, hospital, and other authorities, to whom grateful acknowledgment had been made. The North Midlands Faculty was the first faculty of the College to have been invited by a university—the University of Sheffield—to send a representative to sit on its medical student selection board. Reports from the research committee, the undergraduate and postgraduate education committees, and the Board of Censors all showed much progress. The chairman thanked the Scottish council for the excellent work it had done on behalf of the College in Scotland. A register of members of the College willing to teach students was being prepared. The response to the questionary on the continuing education of family doctors had exceeded expectations. A suggestion had been made that next year the James Mackenzie Lecture, the annual general meeting, a College dinner, and various conferences might possibly be expanded into a clinical week arranged to coincide with hospital postgraduate courses and perhaps with the Medical Exhibition.

### Elections and Presentations

Dr. W. N. Pickles was re-elected president of the College for 1955–6 on the proposal of Dr. J. G. Ollerenshaw, Dr. J. M. Henderson seconding.

The Butterworth Gold Medal was presented to the College, in a gracious speech, by Mr. J. W. Whitlock (managing director of Messrs. Butterworth, Medical Publishers) for an essay on "The Influence of Home Conditions on the Physical and Mental Health of Children During their First Five Years of Life." Dr. D. W. MacLean, of Edinburgh, was awarded the medal and a set of the *British Encyclopaedia of Medical Practice*; Mrs. Beatrice Watts, of Ibstock, Leicestershire, won the second prize. The president expressed the College's grateful thanks to Messrs. Butterworth for these generous annual presentations. The subject for the 1955–6 Butterworth Gold Medal and Award will be announced early in the New Year. Dr. R. J. Minnitt, of Liverpool, was presented with the Foundation Council Award (1955), a small silver gavel on an ebonized base, for "work of the highest merit in the realm of general practice."

The following faculty representatives were appointed to the third College council (1955–6):

L. W. Batten (North London Faculty), H. H. A. Elder (South London), E. A. W. Marien (East London), Annis Gillie (West London), G. Swift (South-east England), J. C. T. Sanctuary (Northern Home Counties), W. G. Tait (Thames Valley), D. Scott Napier (East Anglia), R. M. S. McConaghey (South-west England), D. L. Crombie (Midland Faculty), K. M. Foster (North Midlands), R. A. Murray Scott (Yorkshire Faculty), S. Freeman (North-west England), R. Harkness (North-east England), K. M. Cobban (Merseyside and North Wales), J. N. M. Parry (Welsh Faculty), R. Scott (South-east Scotland), W. S. Gardner (West Scotland), J. M. Henderson (East Scotland), G. Swapp (North-east Scotland), K. A. Mackay (North Scotland), J. Campbell Young (Northern Ireland), L. Masterson (East of Ireland), J. P. J. Little (West Ireland), and W. A. Conolly (New South Wales). (Representatives from the other overseas faculties will be appointed later.)

Twelve members were elected by ballot:

G. F. Abercrombie (North London Faculty), G. O. Barber (Northern Home Counties), J. Fry (South-east England), I. D. Grant (West Scotland), J. H. Grove-White (South-west England), H. L. Glyn Hughes (South London), J. H. Hunt (South London), J. M. Hunter (Northern Ireland), F. Charlotte Naish (North-east England), R. J. F. H. Pinsent (Midland Faculty), F. M. Rose (North-west England), and G. I. Watson (South-east England).

### Constitutional Changes

The College By-laws were amended as to (1) annual subscriptions from members reaching the age of 65; when both husband and wife are members of the College; from members of the Armed Forces; and in cases of hardship; and (2) the formation of a council of the College in Australia and, if requested later, similar councils in Eire and New Zealand.

Votes of thanks to Dr. Abercrombie and the second council were acclaimed, and the chairman thanked the British Medical Association for its generosity in allowing the College to use its Hall. At a meeting of the third College council, held later, Dr. G. F. Abercrombie was elected chairman, Dr. F. M. Rose vice-chairman, Dr. H. L. Glyn Hughes hon. treasurer, and Dr. J. H. Hunt hon. secretary. Dr. W. V. Howells (Welsh Faculty) was appointed as an additional member of council.

## ANNUAL REPORT

The third annual report of the College of General Practitioners is a 250-page volume. The *Register* of members and associates and the faculty lists account for over half of it. The remaining 120 pages are divided about evenly between the report proper, the reports of the 27 individual faculties (Appendix I), and four other appendices. At the end of September, 1955, the College had on its *Register* 2,735 members and 552 associates, a rise of 320 during the year. The principal subjects discussed in the report, besides the year's progress, are undergraduate and postgraduate education, research in general practice, and criteria for membership of the College. A final section records the work of the Scottish council.

There are 22 faculties in the British Isles and five overseas. Of the latter, two are in Eire, two in Australia, and one in New Zealand. Four more overseas faculties are now being formed. The report records the great progress in the development and work of the faculties. In all the three main activities of the College—undergraduate education, postgraduate education, and research—the home faculties have taken an active part, the Scottish council acting as co-ordinator for the work of the faculties in Scotland.

### Medical Education

In the undergraduate field, the report states that there are few medical schools now in the British Isles in which students are not introduced by general practitioners to some aspects of general practice, but there are still difficulties in the way of students who wish to visit a general practice. The College is therefore preparing a register of general practitioners who would be willing to take such students. In April the College council submitted, by invitation, recommendations on the medical curriculum to the General Medical Council. These are printed as Appendix III of the report. In addition the council suggested that, as a first step towards the establishment of departments of general practice in all medical schools, an "observer from general practice" should be appointed to each school. The report records that members and associates of many faculties are already taking students into their practices; others are lecturing in medical schools, and in East Scotland general practitioners are taking ward rounds.

The continuing education of every member is one of the College's primary aims. With this in mind a detailed questionary has been sent to all members and associates to determine their educational habits, needs, and opportunities. The report states that, so far as is known, such material about general practice has never been assembled before. The training and opportunities of the general-practitioner obstetrician have been studied, and the symposium reported at page 141 of this week's *Supplement* was arranged to air this subject. The report states that the number and variety of postgraduate courses for general practitioners are increasing rapidly, and here the faculties have played an important part in both organizing and publicizing such courses. Faculties have also arranged lectures, clinical meetings, ward rounds, and symposia.

### Research in General Practice

The College has developed a strong research organization, both centrally and in the faculties. There is a College research committee, a research register of those engaging in research, a periodical newsletter to keep workers informed of the progress of investigations, and now there are plans for a new records unit. This last would provide opportunities for continued observation of morbidity trends in the community, a project that is also interesting the department of medical statistics at Birmingham. Besides the numerous faculty and individual investigations, the College itself also sponsors research schemes. These include: the assessment of chemotherapy in the prevention of complications of measles; (with the Registrar-General's Department) a national morbidity survey; preparatory work for clinical trials of therapeutic substances; an epidemic observation unit to chart the epidemiological behaviour of selected infections; and a long-term study of the natural history of asthma.

Other matters included in the report are accounts of the work of the board of censors which scrutinizes applications for membership or associateship, and a report of the committee appointed to consider the question of a "membership examination." Such an examination is held by the committee to be practicable, and the committee gives details of its possible scope and organization.

## Preparations and Appliances

### A SUPPORT FOR THE BOYLE-DAVIS GAG

Mr. JOHN MUSGROVE, London, W.1, writes: Several devices for supporting the Boyle–Davis gag during tonsillectomy have been described, but various difficulties are encountered in their use. The support illustrated consists of a right-

angled bracket capable of attachment by a fitting to any type of operating table, the height being readily adjustable by means of a ratchet. When desired, anaesthetic gases can be delivered to the gag through the lumen of the bracket (the upper part being tubular), as shown. In a long trial period this support has proved entirely satisfactory.

The apparatus has been made for me by A. Charles King Ltd., 27, Devonshire Street, London, W.1.

# Correspondence

### Age and Fecundity

SIR,—In discussing the influence of maternal age on fecundity (*Journal*, November 12, p. 1159) Professor Dugald Baird refers to an analysis based upon marriages in England and Wales in 1939 which shows that the proportion of women who were childless ten years after marriage fell very rapidly with increasing age. Even if we assume (*a*) that women who had no children within ten years after marriage remained childless, and (*b*) that contraceptive practice is unrelated to age at marriage, there are other objections to the use of these data as a measure of the rate of decline of fecundity. In the first place age at marriage is not unrelated to fecundity; the proportion of women who marry when they are already pregnant is high for young wives, and falls very rapidly with increasing age. In England and Wales in 1939 the proportions of women who had their first child within eight months of marriage were 73.5%, 32.7%, and 11.2% for women married at ages under 20, 20–24, and 25–29 respectively. The other important consideration is the unrepresentative character of the reproductive histories of women married in 1939; the first publication by the Registrar-General of the material required for a cohort analysis unfortunately coincided with the outbreak of war.

A more accurate indication of the change in fecundity with age is provided by data given in the *Report on the Family Census of 1946*.[1] The report gives the proportions of women in rural Ireland married 30–35 years who were childless at the time of the 1911 Census. The results are here compared with those based upon the 10-year experience of 1939 English marriages.

*Percentages of Childless Women*

| Marriages at Ages | 16–20 | 21–25 | 26–30 | 31–35 | 36–40 | 41–45 |
|---|---|---|---|---|---|---|
| English data (1939 marriages) | 8 | 20 | 30 | 45 | 70 | 90 |

| Marriages at Ages | Under 20 | 20–24 | 25–29 | 30–34 | 35–39 | 40–41 |
|---|---|---|---|---|---|---|
| Irish data (1911 census) .. | 3·6 | 4·4 | 4·9 | 8·5 | 14·7 | 38·0 |

Particularly when it is recognized that age of marriage is not unrelated to fecundity, the Irish data indicate that the decline in fecundity is relatively small until after the age of 30. The same data also show that mean numbers of live births were 8.8, 8.0, 6.8, and 5.6 for women married at ages under 20, 20–24, 25–29, and 30–34 respectively. Moreover, these differences in numbers of live births cannot be attributed wholly to a decline of fecundity, since the shortening of the reproductive period (by approximately five years from one age group to the next) would result in a reduction in the mean number of live births even if fecundity remained unchanged.

Since there is no reason to suppose that fecundity has declined during the present century (the best evidence on this matter is contained in the *Report on an Inquiry into Family Limitation and its Influence on Human Fertility During the last Fifty Years*, by E. Lewis-Faning[2]) the difference between the results of the 1911 Irish Census and those from the 1939 English marriages is almost certainly attributable to the greater use of contraceptive measures at the later period. This was the conclusion reached by Glass and Grebenik in their examination of the increased incidence of childless marriages in England and Wales during the present century.[1]—I am, etc.,

Birmingham. THOMAS MCKEOWN.

REFERENCES

[1] Royal Commission on Population: Report on the Family Census of 1946, 1954, vol. 6. London.

[2] Lewis-Faning, E., Royal Commission on Population: Report on an Inquiry into Family Limitation and its Influence on Human Fertility During the Last Fifty Years, 1949, vol. 1. London.

## Air Embolism During Blood Transfusion

SIR,—Mr. C. Langmaid and Professor W. W. Mushin (*Journal*, November 5, p. 1142) have done a real service by drawing attention once again to the danger of air embolism during transfusion. During intravenous transfusions such embolism, although common, is not often fatal because of the large quantity of air required to produce this result. When, however, a transfusion is given into the right radial artery, as is sometimes done now, a very small quantity of air will pass straight into the carotid artery and produce immediate death. I have seen this happen.

I am afraid that the safeguards suggested are not sufficient. One cannot rely on an assembly of tubing being leak-proof. In my view, no form of pump producing negative pressure anywhere in the system is safe. Therefore the only method of forcing in fluids is the application of positive pressure to the whole system under the unremitting observation of a doctor skilled in this method, whose sole responsibility is the transfusion set while any pressure remains in it.

In addition, but not as the main line of defence, a special drip chamber with a "safety float," as described by Macintosh and Pask,[1] and Wilkinson,[2] should be used. Only complete freedom of the apparatus from any negative pressure and the constant vigilance of the operator will prevent these tragic accidents, most of which have not been reported.—I am, etc.,

Oxford. G. J. FRAENKEL.

REFERENCES

[1] Macintosh, R. R., and Pask, E. A., *Lancet*, 1941, 2, 10.
[2] Wilkinson, C. F., *J. Amer. med. Ass.*, 1951, 146, 1318.

## Attempted Suicide

SIR,—Some guide to the amount of acute mental ill-health in the community can be obtained by a study of the admission rate of attempted suicides to general hospitals and illustrates the importance of teaching psychiatry in the medical schools (Dr. Desmond Curran, *Journal*, August 27, p. 515, and Sir David Henderson, *Journal*, August 27, p. 519). Last year 50 cases of attempted suicide were admitted to the general hospitals of this group, which serves an industrial population of approximately 200,000. Of these one died, 46 recovered after they had received medical and psychiatric treatment at the general hospitals and after-care from the mental health service, and 3 cases were admitted to the local mental hospital. These figures do not include the number of successful suicides, 57 in Glamorgan last year, or the number of attempted suicides treated by the general practitioners. Twenty years ago the number of attempted suicides seen in a general hospital was small, now it is not uncommon to see half a dozen in a couple of weeks, nearly all barbiturate poisonings.

There is still a fear of seeking expert advice in psychiatric illnesses, and I wonder whether some special organization could be set up to which anyone in a desperate state of mind, from any cause, could apply and be sure of obtaining sympathetic and confidential aid, similar in its crude outline to the emergency services of the police or fire services. It would be exposed to abuse, but if it saved any lives and put many others in touch with the appropriate mental health, medical, religious, or social service, it would be a step in the right direction.—I am, etc.,

Church Village, Glamorgan. T. S. DAVIES.

## Organization for Major Disasters

SIR,—I am gratified that Dr. W. N. Leak (*Journal*, November 5, p. 1144) has reopened in your columns the question of the medical organization necessary to cope with major disasters. Like him, I have seen something of the problems involved (I was placed in charge, for twelve hours, of the medical arrangements at Harrow and Wealdstone). But my own experiences lead me to join issue with him on some points.

He considers that the choice of a registrar to lead the mobile surgical unit is "the worst . . . that could be made," and would prefer the duty to devolve upon a senior surgeon. Surely, though, two of the most important considerations in appointing such a leader are (*a*) his immediate availability when the necessity arises, and (*b*) his possession of a considerable degree of physical stamina and agility when he reaches the scene of the accident. On both counts, I think many registrars are more fitted for the task than some of their senior colleagues. I must agree with Dr. Leak that they are, as the years go by, less likely to have had the valuable battlefield experience of the consultants. But the great majority of registrars have completed a period of National Service, and during this time have been instructed in how to deal with major casualties in large numbers. Even in peacetime—particularly if they have served overseas—they will often have had to cope with at least a few serious accidents, and these, very often, under field conditions. A surgeon of registrar status seems to me the obvious and fitting choice for the task under consideration. And—if there is one on the staff of the hospital concerned—the orthopaedic registrar, with his special experience of the surgery of trauma, will usually be the ideal leader.

Furthermore, I cannot see that the absence of a registrar, sent to the actual scene of the disaster, is going to be acutely felt at his hospital. For, when the casualties reach there, their urgent need will be resuscitation and dressing—tasks which can be very effectively performed by the anaesthetic and medical staff (very few of the victims of the Harrow disaster could be operated on before several hours had elapsed, and many, in fact, were not taken to the operating theatre until the night of, or the morning after, the day of the collision).

But no matter who leads the mobile surgical team, it is in hospital that the majority of lives and limbs will be saved. I am therefore surprised to find that Dr. Leak decries the part that the management committees have to play in planning for these catastrophes. A considerable amount of forethought is required if the victims are to be treated rapidly and correctly. Several years ago, I saw a large, and normally efficient, hospital severely disorganized by the sudden arrival of only fifteen or twenty casualties from a nearby bus smash. It is high time that each management committee was charged with drawing up, at least in outline, a plan of the action its institution proposes to take if confronted with a similar or larger number of casualties—where they would be received, where extra beds are to be put up, and which members of the staff would be charged with their care. Only by such forethought can we hope to avoid the repetition of such a pitiful scene as I once witnessed—row after row of stretcher cases lying on the floor of a hopelessly inadequate receiving room, while doctors and nurses stepped hither and thither over them, colliding with one another in a frustrated effort to restore order out of chaos.—I am, etc.,

London, W.C.1. RICHARD HARRISON.

## Protection of Infants Against Tuberculosis

SIR,—Professor Wilfrid Gaisford's Leonard Parsons Memorial Lecture on the above subject (*Journal*, November 5, p. 1101) is of such outstanding interest and brilliance that it is with some hesitation that one ventures to challenge him on two relatively minor points.

Professor Gaisford alludes to Zeidberg's study,[1] in which he compares the incidence of tuberculosis in infants in homes where the sputum-positive case was a parent with the incidence in homes where the sputum-positive case was not a parent but a less-nearly related member of the family, and he comes to the surprising conclusion that "therefore the contact was equally intimate in the two groups." Does Professor Gaisford seriously suggest that the contact of an infant with a maiden aunt, an uncle, or a big brother is in any way comparable in intimacy with that of a mother or even a father?

Professor Gaisford, in a sanely reasoned plea for vaccination of infants against tuberculosis, asks, "Is it not a fact that in the case of smallpox [the low death rate in this country]

is directly due to the efforts of the vaccination enthusiasts of the past?" The answer is surely, quite definitely, no; it is not a fact, and no epidemiologist of the mid-twentieth century would make such a claim. Individual vaccination gives complete and temporary protection to the individual vaccinated, but mass infantile vaccination has never had any appreciable effect on the size of epidemics, admittedly partly because it has never been practised. Let us take the present half-century. The vaccinal state of infants was higher from 1901 to 1905 than at any time in our history. In 1901 no fewer than 71.4% of our infants were vaccinated, and this had increased in 1905 to 75.8%, the highest in our history. As these were infant vaccinations and their immunity would wane in adult life, it would be reasonable to assume that less than one-third of our population were protected during the quinquennium of heaviest vaccination. During the five years from 1948 to 1952, the percentage of infants vaccinated in this country fell to an all-time low. In the six months after July, 1948, the figure fell to 18.2%. But from 1901 to 1905 there were 4,203 deaths from variola major, whereas in a much larger population in 1948–52 there were 16 deaths and 54 cases.

Professor Gaisford uses the words "scourge of smallpox." If we define a scourge as an epidemic of infectious disease with a death roll of, say, 100, then there has been no scourge of smallpox since 1905, the year of peak infant vaccinations in this country. No, smallpox in this country is checked and controlled, when it does enter, by the early diagnosis and removal of the patient, and the supervision and vaccination of all contacts.

These facts do not invalidate Professor Gaisford's main argument in favour of vaccination of infants against tuberculosis. The epidemiology of the two diseases is different, in that the mycobacterium is ubiquitous in this country whereas the virus of smallpox is not.—I am, etc.,

Bournemouth. HUGH PAUL.

REFERENCE

1 Zeidberg, L. D., Dillon, Ann, and Gass, R. S., *Amer. Rev. Tuberc.*, 1954, **70**, 1009.

## Besnier's Prurigo

SIR,—Your excellent annotation (*Journal*, November 5, p. 1134) is a review of the symposium given at the annual meeting in Cambridge, 1954, of the British Association of Dermatology, and subsequently published in the association's journal.

As one who was partly responsible for the choice of subject and speakers I write to express my sense of gratitude and appreciation, no doubt shared by my colleagues, for this thoughtful and stimulating presentation of their views. It is particularly valuable because it shows that, in spite of their widely differing approach to the subject, the five papers do present different facets of the same problem, and contribute each in their own way towards a better understanding of the eczema–asthma–hay-fever groups of disorders.

The conclusion in your penultimate sentence that "the fundamental defect involves the whole patient" is not new and was in fact reached many years ago by discerning British dermatologists such as Gray, Barber, and others, yet its reiteration can do nothing but good, if only in reminding us once more that treatment which is confined to the surface is apt to be superficial in more senses than one.—I am, etc.,

Cambridge. C. HOWARD WHITTLE.

## Acute Pancreatitis

SIR,—I have read Mr. Robin Burkitt's letter on acute pancreatitis (*Journal*, November 12, p. 1210) with interest. On what evidence does he state that there are "two entirely different diseases, both of which go by the name of 'acute pancreatitis'"? In my experience of emergency surgery, which is also considerable, I have seen every gradation between the mildly swollen pancreas with a few specks of fat necrosis and the black necrotic organ. Why also does he state that "the serum amylase level naturally varies with the degree of fat necrosis"? Does it not depend on a balance between obstruction and destruction?—I am, etc.,

London, W.1. HENEAGE OGILVIE.

## Chlorpromazine and Jaundice

SIR,—I found the paper on jaundice in relation to chlorpromazine therapy by Dr. B. Isaacs *et al.* (*Journal*, November 5, p. 1122) arresting, but I cannot subscribe to the view that the features of the jaundice are supported by either Boardman[1] or Lomas *et al.*[2] In fact, the implications of this paper constitute a rebuttal of the pathogenesis suggested by Lomas *et al.*—namely, sensitization.

The biochemical findings were similar, but if we look at the aetiology what do we find in the Isaacs series? (1) The earlier occurrence of jaundice after commencement of treatment in all but the fourth case—that is, 6th, 4th, <14 day. Lomas: 16th to 35th. (2) In three of four cases the drug was not being given at the time when jaundice appeared. Lomas: "No case arose after completion of therapy." (3) The markedly shorter period of drug administration—that is, 6, 2, 2, 7 days. Lomas: minimum 16 days.

It is largely from the fact that the only reasonably constant factor appearing in chlorpromazine jaundice studies is its relationship to length of treatment that the sensitization hypothesis arose, which hypothesis appears to have a strong body of support in this country and the U.S.A. If we accept the Isaacs series as the product of chlorpromazine the hypothesis falls down, and two cases developed jaundice on the sixth and the fourth days, the latter having received the drug for two days only, which hardly allows time for sensitization to occur. If we now view cases (1) to (4) with a harshly critical eye, we find well-established malignant disease in (1) and (2), and antecedent liver disease in (2) and (3); furthermore, (1) and (2) were on "large-dose oestrogen therapy" for carcinoma of the breast. The significance of this I cannot guess at, but had these cases by any chance previously had testosterone therapy? For my information on American work is that testosterone jaundice gives a liver histology identical with that of chlorpromazine jaundice (with which incidentally case (2) does not appear to conform). Although these three cases are confused by extraneous aetiologies, case (4), introduced from without the Isaacs series, is stimulating. As the authors imply, it is impossible to exclude infective hepatitis, but this woman became jaundiced on the 20th day after commencing a seven-day course of chlorpromazine. We know that this drug is still excreted after four days,[3] making at least eleven days during which the internal environment includes chlorpromazine. This is probably an adequate period for sensitization.

My concern with this affair is that in clinical psychiatry I find chlorpromazine a most valuable asset. Therefore I need to have a knowledge of its hazards and a working hypothesis on its principal one, jaundice. If the implications of this paper are valid, I and many others will have to think again. If my criticism is valid, it will, I hope, allay the many fears that this paper gives birth to.—I am, etc.,

London, S.W.17. R. H. BOARDMAN.

REFERENCES

1 Boardman, R. H., *British Medical Journal*, 1954, **2**, 579.
2 Lomas, J., Boardman, R. H., and Markowe, M., *Lancet*, 1955, **1**, 1144.
3 Trutschel, W., *Acta hepat.*, 1955, **3**, June.

## Rauwolfia Serpentina

SIR,—I have lately noticed, with some apprehension, that the sedative properties of rauwolfia serpentina, which cannot be divorced from its hypotensive action, have brought this potent drug outside the ethical frame and on to the screen of public advertising in the lay press, advising its use in anxiety states, tension, worry, etc.

It has been observed that patients particularly sensitive to rauwolfia respond with too rapid a fall in blood pressure

with consequent giddiness, fainting, and even some mental confusion. Furthermore, it is well known that rauwolfia can have toxic side-effects of no small order, sometimes resulting in the opposite of what it is intended to do—for example, excitement or depression where emotional stability is the aim. The sudden drop in blood pressure can also take place in normotensive patients, as experienced in my own practice in the case of a woman who was taking "tranquilex" tablets for several days with resulting vertigo, lassitude, and depression. Discontinuation of the tablets and two days' rest were sufficient to remove the ill effects. The patient was introduced to this preparation by an advertisement.

There is great danger in persuading the general public to employ self-medication with drugs of fairly recent discovery whose properties have neither yet been definitely assessed nor found to be innocuous. It is my humble opinion that rauwolfia and its alkaloids ought to be obtainable only on a doctor's prescription and administered under strict medical control.—I am, etc.,

London, N.W.2. H. MARGULIES.

*** As announced elsewhere (p. 1340), the manufacturers of "tranquilex" are ceasing to advertise this drug to the public.—ED., *B.M.J.*

## Expression of the Sickle-cell Gene in Africa

SIR,—We have recently reported[1] the finding, in the course of a survey, of two individuals who were not suffering from sickle-cell anaemia but whose haemoglobin was indistinguishable from that of homozygotes for the gene responsible for sickle-cell haemoglobin. On electrophoresis no adult haemoglobin (A) was discovered, and a fraction was resistant to alkali denaturation—indicating the presence of foetal haemoglobin (F). The solubility of the reduced haemoglobin in phosphate buffer also fell within the range known for haemoglobin derived from homozygotes for the sickle-cell gene or from heterozygotes for the genes responsible for adult and sickle-cell haemoglobin (S) in whom the production of haemoglobin A was suppressed as an expression of a thalassaemia gene (sickle-cell-thalassaemia). In that condition the amount of haemoglobin A produced can be so small that it may escape detection by electrophoresis. The condition in which the haemoglobin mixture AS is accompanied by the possession of a thalassaemia gene is called sickle-cell-thalassaemia.

We stated "a sickle cell homozygote with a high percentage of foetal haemoglobin and a sickle-cell-thalassaemia individual may not be differentiated by electrophoresis (though this will be exceptional), and the solubility of the two haemoglobin mixtures may be within the same range, the upper range for that seen in SS homozygotes. If such a finding is made the only recourse is still the family study." However, we thought it unlikely that sickle-cell-thalassaemia could occur in the Gold Coast, as thalassaemia itself had never been observed in Gold Coast Africans. We have now to report that family studies in these two individuals have brought to light the fact that a thalassaemia-like gene is present in the Gold Coast. Both the propositi had non-sickling children and each had one child which, though well beyond the age of infancy, had appreciable amounts of foetal haemoglobin in its red cells. The genes for haemoglobin A and S and the gene for thalassaemia are inherited independently. Thus the finding in these two offspring is one which would be seen in individuals who inherited a gene for haemoglobin A and one for thalassaemia (thalassaemia minor). However, their blood films showed no target cells or only very occasional ones and there was no microcythaemia. Though some individuals in this study had a raised red-cell resistance to hypotonic saline there did not seem to be a correlation between this feature and the presumed presence of a thalassaemia or thalassaemia-like gene.

*Families of J. A. S. and E. B. A. D.*[1]

| | Hb g.% | Haemoglobin Pattern | Foetal Hb % | M.C.V. cu.$\mu$ | Target Cells | Reticulocytes % | 50% Haemolysis at % Saline |
|---|---|---|---|---|---|---|---|
| Propositus J. A. S. | 11·9 | SS+F | 5·9 | 81 | Scanty | 1·2 | 0·42 |
| Adult daughter | 12·2 | AA+F | 5·0 | 82 | Nil | 2·4 | 0·50 |
| 12-year-old son .. | 13·6 | AC | — | 74 | ,, | 1·2 | 0·34 |
| Propositus E. B. A. D. | 14·5 | SS+F | 26 | 89 | Scanty | 0·6 | 0·33 |
| Wife .. | 12·7 | AA | — | 83 | ,, | 0·2 | 0·38 |
| 4½-year-old son .. | 9·6 | AA+F | 24 | 93 | ,, | 1·0 | 0·37 |

There is no reason why the children in the two families should not be legitimate. Blood group determinations were performed by Miss E. W. Ikin in Dr. A. E. Mourant's laboratory; there was no indication of non-paternity. Indeed the finding of foetal haemoglobin but not of sickle-cell haemoglobin in one offspring of each propositus would confirm that the sickling parents were sickle-cell heterozygotes with one thalassaemia gene. In the son of propositus J. A. S. the haemoglobin mixture was one of A and C haemoglobins. As the C haemoglobin cannot have been inherited from the propositus it is almost certain that the latter must be a carrier of the gene responsible for the A haemoglobin. We hope to discuss these findings more fully in due course, but as they invalidate some of the genetical conclusions put forward in our original article we have thought it right to present them as soon as possible in this letter. Meanwhile it remains a fact that normal adults may have proportions of sickle-cell and foetal haemoglobin in their blood which at the present time cannot be distinguished by chemical or physical means from those seen in patients with sickle-cell anaemia.—We are, etc.,

Accra, Gold Coast. G. M. EDINGTON.
London, E.C.1. H. LEHMANN.

REFERENCE

1 Edington, G. M., and Lehmann, H., *British Medical Journal*, 1955, 1, 1308.

## Paroxysmal Ankle Pains

SIR,—Paroxysmal ankle pains of the type I am considering must not be very rare among middle-aged and elderly individuals, especially those temporarily confined to bed owing to an attack of influenza or some other ailment. The affected persons are often somewhat emaciated or have defective circulation in the lower extremities, owing to atheromatous or other changes, including thrombo-angiitis obliterans in the arteries supplying the legs. These patients may occasionally also suffer from ordinary muscular cramps of the calf and plantar muscles and intermittent claudication, which confuses the patient in describing his symptoms to the doctor.

The attacks may be spoken of as ankle cramps or peroneal cramps, but they are not true muscular cramps, though I regard them as paroxysmal pains, almost certainly of ischaemic nature. The patient may wake up in the night from a good sleep, feeling severe pain in one ankle, which he soon perceives is not due to ordinary muscular cramp. Nevertheless, he will probably with some difficulty get out of bed. Then he finds that the ankle pain is increased by standing on the affected leg and seems not to be passing off. However, after a time the pain invariably does pass off and may not return, at all events for a long period. The probability is, as I have already stated, that the pain is of ischaemic origin and may be avoided by paying attention to the position of the limb in bed and preventing continued pressure on the peroneal (fibular) region on a rather hard mattress.

Though the trouble in question is undoubtedly more common than I formerly supposed, I have not met with satisfactory accounts in ordinary textbooks. I have myself only once scantily alluded to it.[1]—I am, etc.,

London, N.W.1. F. PARKES WEBER.

REFERENCE

1 Weber, F. Parkes, *On Naevi and Miscellaneous Subjects*, 1952, p. 57, footnote 19. London.

## Safety-helmets

SIR,—It is accepted that the wearing of safety-helmets by those riding on motor-cycles greatly decreases the mortality and serious injury rate among those involved in accidents. It is comforting to see the large increase in their use in the last few years—originating from a campaign started by the late Sir Hugh Cairns, helped by the national press. Two things are discomfiting: first, it is estimated that out of 1,000,000 riders of motor-cycles in this country still only 25% wear helmets regularly. Secondly, one aspect has been overlooked: it is exceedingly rare to see children passengers wearing safety-helmets in this country. After a year's residence in France, where safety-helmets are almost universally worn, it was noted that children are frequently carried as passengers. Good safety-helmets and protective clothing are readily obtainable in children's sizes, and it is rare to see them not properly equipped.

In three recent Sunday afternoons on English main roads 115 motor-cycles with and without sidecars were counted which carried children (approximately 15 years and under). One child was properly equipped. None of the others were. Approximately 800 child passengers of motor-cycles were injured last year in accidents in this country. Recently two boys, of 12 and 14 respectively, were seen in hospitals with severe head injuries. They had been pillion passengers and involved in motor-cycle accidents. It was the opinion of the surgeons concerned in their care that neither would have suffered severe injury had they been wearing safety-helmets. There is only one firm in this country, to my knowledge, which advertises the fact that it sells children's helmets. The approximate price is £3, and this includes 15% purchase tax.

It is argued by some responsible people that the child has no place as a passenger upon a motor-cycle, and further that the introduction of safety-helmets for their use might encourage the carrying of more children. This argument cannot be accepted. Children in significant numbers *are* carried as passengers, and we should protect them as much as possible while this is so. The example of our French neighbours should surely be followed. I am in complete agreement with the opinion expressed in that delightful letter written to Sir Hugh Linstead, M.P., which was published in the *Supplement* of July 23 (p. 33); in a word, surely it is partly a medical responsibility. Sir Hugh Linstead's correspondent put it much better than that.—I am, etc.,

London, W.C.1. FRANK FALKNER.

## Physiotherapy

SIR,—We write to raise a number of questions about present-day physiotherapy, and to make suggestions about its future.

It is often claimed that inducto-thermy treatment gives different results from short-wave therapy. Does it? If it does not, should not the simpler and less costly method be used? Is it a fact that short-wave treatment of chronic antritis is of general clinical value? Could not a consensus of clinical and radiological opinion be gained as to exactly how much value it is and under what circumstances it is warranted? Is it a fact that inducto-thermy relieves some of the symptoms of coronary thrombosis and improves the prognosis? If so, on what physiological basis does such treatment rest, and does the E.C.G. support this claim? Is there any advantage over an ordinary gas fire in the use of special apparatus designed to give a supply of infra-red radiation?

Is there any unique therapeutic value in ultra-violet radiation when the emission comes from a particular metal? Some years ago it was claimed that a new variety of ultra-violet (S rays) was emitted from tungsten; the claim was unfounded. Lately we are told of the virtues of titanium radiation; these may be classed in the same category. Ultra-violet therapy has had a long innings; at one period healthy people were encouraged to install apparatus in their own homes and revel in the exposure of their healthy bodies to this dangerous radiation. If some bodily conditions are benefited by a little irradiated ergosterol, would it not be much simpler to give it by mouth or by injection than engage extra staff in hospitals to wield expensive apparatus?

For some years the subject of radiotherapy suffered from the fact that it was carried out on a basis of empiricism; gradually people began to investigate the nature of cellular and tissue reactions to radiation, with widespread benefit to the practitioner and to the patient. Is it not likely that if the same quickening spirit could animate the subject of physiotherapy it would help to provide a physiological base upon which this very important form of medical treatment could be more securely and faithfully built?

The few examples we have cited invite the reflection that the time has come for an impartial assessment of the whole range of treatment that is carried out in the name of physiotherapy. We suggest the formation of a committee, preferably by the Ministry of Health, to report upon the present position and to outline the steps that could well be begun now to usher in a new era for this subject.—We are, etc.,

C. B. HEALD.
Chipping Camden, Glos. SIDNEY RUSS.

## Munchausen Syndrome

SIR,—We have followed with great interest the correspondence arising from our memorandum (*Journal*, Octo-29, p. 1068) and we should like to thank the large number of doctors who have communicated with us personally. From some of the latter we learned that our patient visited five different hospitals in the five days following publication. It says much for the circulation of the *Journal* that he was rapidly recognized at most of these hospitals, and this apparently accelerated his movements from one hospital to the next. At most of these hospitals he complained of severe abdominal pain which necessitated injection of analgesics, usually pethidine; and one doctor remarked on the multiple puncture marks on each thigh. Pethidine relieved the "colic" within two minutes. He has been given, or been prepared for, several blood transfusions, and the usual exhaustive investigations have been carried out.

We have also been made aware of several similar cases now active in the U.K., which makes us realize that the problem is greater than we anticipated. We wonder if any medico-legal advice could be given to doctors who have to deal with these patients. Can certification be considered on the ground that these patients constitute a danger to themselves by repeatedly undergoing diagnostic and therapeutic procedures—for example, lumbar puncture, blood transfusions, and laparotomy? Could the law regarding drug addiction be used in this context? Criminal proceedings by reason of abuse of public funds are unlikely to appeal to the profession in psychopathic cases.

The suggestion of a "rogues' gallery" as put forward by Dr. Ian A. Short (*Journal*, November 12, p. 1206) and Dr. R. E. Irvine (p. 1207) had also occurred to us; but as far as we know no one has succeeded in photographing our patient as Dr. P. B. B. Gatesby (p. 1207) suggests—a recent attempt to do so at Poole was unsuccessful and caused him to discharge himself abruptly. We would certainly be willing to communicate this man's particulars to the *Journal* or the Ministry of Health should they wish to publish them, provided that our medical defence organization approved of such a step.

We must confess ourselves a little puzzled by Dr. M. B. Clyne's letter (p. 1207). We do not feel that in our case report we "complain bitterly," and we can assure Dr. Clyne that, even as rheumatologists, we constantly find "that there are human beings conjoined to their rheumatism"; indeed, it was in the hope that something might be achieved to help this human being, to say nothing of all those other human beings who pay for and work in the Health Service, that we wrote our case report. Dr. Clyne concludes, "We shall in the end just have to try to become better doctors if we want to beat Munchausen." We agree that this is a laudable aim; nevertheless, it is laying a grave responsibility at the

door of the already harassed casualty officer to expect him to label as "functional" an unknown case presenting with a tall (indeed, sometimes not so tall) story and a blood-stained face.

We feel that some form of restraint which would terminate the activities of these unfortunate individuals is certainly in the public interest. Quite apart from the expense involved, they throw a heavy strain on the nursing staff and they frequently cause distress to other patients. Indeed, their only merit from a medical viewpoint is that they may provide an interesting, albeit sometimes humiliating, diagnostic exercise.—We are, etc.,

R. A. GAWN.
E. A. KAUFFMANN.

London, N.W.3.

SIR,—Before your columns are closed to correspondence about that absorbing variant of mankind described again by Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068), may we record that when last seen he was heading east? On the evening of November 8, 1955, bleeding from the left ear and bent double with "clot colic," he ploughed through the usual obstructions to the admission of patients and shortly came to rest in the ward in time for supper. *En route* he had whispered the magic words "AB negative" and, even as he began to unfold his story, all the Rhesus-negative blood in the South-western Region was speeding towards Gloucester Royal Infirmary in an express train. Pathologists kissed their families good night, cortisone stocks were checked, and to the sound of instruments being rattled in the sluice we settled down to listen.

His trouble, he told us, was thrombocytopenia. It was diagnosed in 1950 in the Army, and they quickly took his spleen out, but without effect. After this slighting reference he flourished his arms in the air, displaying myriads of half-inch (1.27-cm.) scars and two recent gaping unstitched "cut down" wounds to demonstrate the difficulty which his physicians have subsequently experienced in keeping him alive with quarterly transfusions. Our gloomy countenances must have spurred him on, for, throwing care and genetics to the wind, he said, "Of course, my father has married twice and my step-brother has Christmas disease." Having thus produced an awed gasp from his audience, he felt himself among friends, and the rest of his history was given with even less care than before.

On clinical examination the mucous membrane of his mouth was covered with ulcers of varying size and depth. Each had a necrotic base and in parts they were confluent. For the record, the recent wounds on the left arm were linear and half an inch (1.27 cm.) long with edges separated by pus, thus forming an ellipse. Their long axes were across the limb, and one was in the mid-forearm on the flexor aspect and the other was on the dorsum of the hand. His ankles were also the seat of many scars. His abdomen and buttocks were similarly marked with old and recent wounds, most of which were small and circular. Old operation scars were as described by Dr. P. B. B. Gatenby (*Journal*, November 12, p. 1207). There were no skin lesions on any part not easily accessible with either hand. Dried blood was present on the left ear and he appeared "uneasy" during auroscopy. His urinal contained evenly blood-stained urine. His facial expression, his behaviour, and his words labelled him as an obvious liar. His normal bleeding and clotting times and peripheral blood did not suggest any organic basis for his malingering. His blood group was AB Rhesus positive and his Wassermann and Kahn reactions have since been shown to be negative.

His case provoked a most stimulating discussion on "bleeders," and such was its duration that when we returned to the ward the man was sleeping soundly. It seemed a shame to waken him and throw him out into the rain, especially as his urethra must have been very sore, and so it was decided to leave him for the night. The following morning, when the streets were aired, he offered us his thanks and took his discharge.—We are, etc.,

G. V. BALMFORTH.
J. A. POLLOCK.

Gloucester.

SIR,—The case of Dr. R. A. Gawn and Dr. E. A. Kauffmann (*Journal*, October 29, p. 1068) reminds me of the most extraordinary deception I have met.

During the war my house-physician telephoned to say he had an intractable case of acute pulmonary oedema in casualty. At the hospital, I found a man with severe dyspnoea, respiration quick, deep, and rattling; pulse quick, slight rise of temperature, and many rales and rhonchi in the lungs. He had already had morphine without effect, and when a further dose did not relieve I did a venesection. The man seemed quite willing and even grateful to have this. After over an hour of deep quick breathing, there was some relief. A little later I looked at his pupils and wondered why they were not contracted after all the morphine he had been given. I then looked at his arms and discovered an extensive blue staining of the skin. I concluded he was a morphine addict, and that he also had chronic bronchitis but no cardiovascular disease. He probably knew how to put the thermometer reading up, and, as he had been a hospital technician, knew about cardiac asthma and that morphine was given for it. But I cannot explain how he kept up the appearance of severe dyspnoea for over an hour.

He was discharged after two days in hospital, when we had confirmed our suspicion and he knew that we had. I heard afterwards that he continued to play his trick on other hospitals.—I am, etc.,

Bournemouth. HAROLD COOKSON.

SIR,—I was interested in the report of Drs. R. A. Gawn and E. A. Kauffmann on a case of Munchausen syndrome (*Journal*, October 29, p. 1068). I came across a very similar case at the Kilton Hospital, Worksop, eight years ago. There a 20-year-old man cut his fingers secretly in the ward-bed and mixed the blood with his urine in the urinal; he was discharged as a malingerer as soon as he was found out.—I am, etc.,

Mansfield, Notts. F. TUCHLER.

*** This correspondence is now closed.—ED., *B.M.J.*

## Carcinogen in Coal-tar

SIR,—I am impressed by the following paragraph in Dr. C. E. Goldsborough's letter (*Journal*, November 12, p. 1209): "At present, although it is illegal, there is no police action taken against lorries which pump out heavy concentrations of exhaust gases." Passing through a provincial city recently, I stopped and complained to a policeman of the exhaust from a lorry on the road on which I was travelling. It was an evil-smelling black cloud like a smoke screen, and as such was obviously dangerous to traffic, quite apart from any ill effects of inhaling it by those whom it enveloped. The constable was most indifferent, merely remarking that "we sometimes see these smoky lorries"; and did not even bother to take out his notebook and record the particulars.

I would hope with Dr. Goldsborough that some action might be taken in these cases not only for the sake of public health but also for that of road safety.—I am, etc.,

Cardiff. LAMBERT ROGERS.

SIR,—The recent correspondence in the *Journal* under this heading from Dr. C. E. Goldsborough (*Journal*, October, 15, p. 969, and November 12, p. 1209) and Sir Ernest Kennaway (*Journal*, October 22, p. 1027) prompts me to make some further comment.

It is not generally appreciated that, however well adjusted and apparently smoke-free a diesel engine may be, invisible soot particles and unburnt fuel oil are always emitted. It is impossible for a compression-ignition engine to run with a mixture ratio of air to fuel that can produce any other condition of exhaust. Furthermore, diesel-engine exhaust contains a much higher proportion of nitric oxide and aldehydes than the exhaust from a petrol engine. Both these irritants are about ten times more injurious to the eyes and

respiratory tissues than sulphur dioxide. It is an unfortunate fact that the emission of these combustion products is highest when the engines are decelerating or idling. Therefore in conditions of town traffic one gets a much more dangerous concentration. Finally, the humidity of the atmosphere in this country tends to concentrate as aerosols these acids in the lower levels of the atmosphere. Thus in the still, anticyclonic, foggy type of weather this becomes a very serious matter.

While it is true that most of the soot and aerosols may be arrested in the upper respiratory tract, it cannot be denied that some reach deeply into the bronchial tree. A condition of hyperaemia and exudation is set up thereby, which surely enhances the risk of adhesion of the smaller oil–soot particles (under 1 micron) which can penetrate into the bronchi. In fact, does this chronic irritation perhaps favour the subsequent effect of the carcinogen?

It would seem, therefore, that the only means of tackling this very serious menace to health is by filtering the exhausts. This has been successfully achieved in the U.S.A. by the use of a catalytic filter which reduces everything in the exhaust of petrol or diesel engines to carbon dioxide and water. It is to be hoped that shortly legislation will be made for the compulsory use of some similar filter on the exhaust of all public and privately owned internal combustion engines in this country.—I am, etc.,

Bristol, 8. HANDLEY HOWELL.

## Carcinogenic Properties of City Smoke

SIR,—The experiments on tissue cultures of human lung attributed to me in your annotation "Carcinogenic Properties of City Smoke" (November 19, p. 1261) are being carried out by Dr. Ilse Lasnitzki at the Strangeways Memorial Laboratory, Cambridge, with material prepared here.—I am, etc.,

St. Bartholomew's Hospital, London, E.C.1. E. L. KENNAWAY.

## Ban on Heroin

SIR,—Dr. A. H. Douthwaite in his letter (*Journal*, November 19, p. 1267) writes: "The outstanding lesson of this controversy is that the structure for consultations between the Government and the medical profession is faulty." The implications of the issue raised are significant and far-reaching.

The senior physician of a hospital is, as a rule, the representative of the views of the medical staff, when these are called for: he is, within his own fraternity, *primus inter pares*. Many senior physicians are fellows of the Royal College of Physicians: the latter elect their own president, who is, again, *primus inter pares* among his fellows. The College was, probably, the most puissant medical body; the institution remains, but the power has waned.

Allied callings, as, for instance, the Church and Bar, have a similar administration, and retained prestige. The Archbishop of Canterbury is *primus inter pares* among bishops. The Lord Chief Justice is *primus inter pares* among judges. The same concept of rule is valid for the Throne. The bloodless revolution of 1688 culminated in the Act of Settlement, which affirms that sovereign law resides with the king in Parliament and not with absolute monarchy.

Authority in medicine is now vested in the absolute power of the Minister of Health. The notion of *primus inter pares* has been abandoned in favour of primacy. If the Act of Settlement still denotes the community sense of the majority, the National Health Act has, in this respect, put the clock back two and a half centuries.

The ban on heroin is but one sample of what may happen under the prescript of the divine right of the Minister of Health. Those who, like Dr. Douthwaite, have the confidence of practitioners will, it may be presumed, in considering "the structure for consultations," bear the two following facts in mind: the current constitution is, in contrast to the Church and Bar, archaic; and at variance with the tenets of freedom as asseverated in the Act of Settlement. *Delenda est primatia.*—I am, etc.,

London, W.1. MURDO MACKENZIE.

## Visit of Russian Doctors

SIR,—On December 1, 1951 (p. 1337), you published a letter in which I proposed that the B.M.A. should invite Russian doctors to visit us, and on March 8, 1952 (p. 548), I explained that the object of my proposal was to take the first step in the prevention of wars. The fact that the great weight of a leading article was not put into the scales did not surprise me because I had had the greatest difficulty in persuading you to publish anything at all, but it must have surprised a great many members and it did seem rather a pity that it should be left to the *Manchester Guardian* to deal with a matter that concerned the B.M.A.

About five months ago I sent you another letter with the same object. I had been deeply impressed by an account, which had then just been published, of the martyrdom of a German medical student, his young sister, and four friends. I thought that perhaps the medical students in this country might feel that a unique sacrifice for freedom ought to be commemorated in some way, perhaps by sending a deputation to Munich, and I hoped that they would agree that freedom is the ultimate remedy against war. But my letter was rejected by return of post, without comment, and without a word about the young Germans.

The policy of the *British Medical Journal* with regard to the prevention of war has been very obscure, but your annotation (*Journal*, October 22, p. 1021) is enlightening. You tell us that the recent visit of Russian doctors "shows once more that when governments allow an easing of tension professional groups of different countries are eager . . . to make those personal contacts which help to brush away the cobwebs of misunderstanding." In other words, what you tell us is that in times of tension and aching anxiety we must realize that the prevention of war is a matter of great difficulty and must be left to our elders and betters; the governments know what is best and we must not interfere by trying to arrange visits; when they allow an easing of tension between east and west in Germany then perhaps the *Journal* will be able to publish letters about eccentrics who get themselves beheaded for the sake of freedom. That seems to be the obvious implication of your annotation, and, taken in conjunction with the difficulty in getting my first letter published and the rejection of the second, it makes me wonder whether there is some form of censorship in the *Journal* office. If not, it is difficult to see why a letter about the killing of German students could not be published. But, however that may be, I am sure that if you will be so good as to publish this letter you will find that many members will be grateful if you will tell us what the policy of the *Journal* is going to be when international tension becomes acute again.—I am, etc.,

Wetherby, Yorks. R. L. KITCHING.

## Hypercapnoea

SIR,—As anaesthetists become ever more physiologically minded we have come to regard as inevitable the sporadic appearance in our textbooks[1] of such strange words as "acapnoea." But when, Sir, your own leading article on hypothermia (*Journal*, November 5, p. 1131) gives its authority to another of this monstrous brood (hypercapnoea), the time has come, it would seem, to draw attention to the manner of their birth and if possible prevent their further reproduction.

One must assume that since apnoea means absence of breathing, and since acapnia, which means absence of carbon dioxide, can give rise to such a state, the mis-spelling "acapnoea" resulted by fusion of ideas; thence by extension "hypocapnoea" arose, in much the same way that it became recognized as more accurate to speak of hypoxia rather than anoxia in most circumstances in anaesthesia; finally, "hypercapnoea" rears its ugly head, conjuring up pictures of an exhausted soda-lime canister, an apnoeic patient, and a respiratory centre poisoned with carbon dioxide.

In fact, of course, the derivation of these words is totally different, and this is, as the dictionaries[2] show us, reflected

in their spelling. Apnoea is from πνοή (breath),[3] acapnia is from κάπνός (smoke and thus carbon dioxide),[3] in each case with the privative alpha prefixed to indicate "absence of." The resulting phonetic similarity is one of those sad coincidences, but also to confuse the spelling must surely be a major disaster for the student confronted with "acapnoea" as a cause of apnoea and apnoea as a cause of "hypercapnoea," which in turn causes hyperpnoea.

In conclusion, should any justification by usage be forthcoming for these (regrettably) cisatlantic[4] solecisms, one can at any rate, Sir, with safety accuse you, if not of inaccuracy, then of inconsistency in not also heading your leader "hyperthermoea."—I am, etc.,

Finchampstead, Berks. H. M. C. CORFIELD.

REFERENCES

1 Lee, J. A., *A Synopsis of Anaesthesia*, 1955, 3rd ed., pp. 27 and 161. Wright, Bristol.
2 *Webster's New International English Dictionary*, 1953, 2nd ed., pp. 13 and 125. Bell, London.
3 Liddell, H. G., and Scott, R., *A Greek Lexicon: Revised Edition*, 1925-1940, pp. 1425 and 876. Clarendon, Oxford.
4 Dorland, W. A. N., *American Illustrated Medical Dictionary*, 1951, pp. 9, 702 and 711. Saunders, Philadelphia.

### Christmas Gifts Fund

SIR,—I would like to remind your readers who have not yet responded to the President's appeal (*Journal*, October 8, p. 906) that it is our custom to distribute the gifts some days before Christmas.

I hope all who can will send their contributions marked "Christmas Gifts" to the Secretary, Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, London, S.W.15, as soon as possible.—I am, etc.,

London, S.W.15. F. A. JULER, Honorary Treasurer.

## POINTS FROM LETTERS

### Food-Poisoning

Dr. P. H. BEVES (London, S.E.22) writes: I am inclined to agree with Dr. P. Mestitz (*Journal*, October 1, p. 854) about foot-pedals for lavatory cisterns, but they would have to be well down. The Navy tends to place them high enough to offer manual operation as a practicable alternative, besides being a hazard to the right buttock when the ship rolls. On the other hand, I do not follow Dr. R. E. Dreaper's argument (*Journal*, October 22, p. 1027). Surely the left hand is the one he uses to pick up his toast and marmalade. Moral: "Government property" may be thicker than "bronco," but it is still as well to wash the hands.

### Penicillin Anaphylactoid Shock

Dr. AYRES L. RIBEIRO (Nairobi, Kenya) writes: I read with great interest the medical memorandum about penicillin anaphylactoid shock successfully treated with adrenaline (*Journal*, September 17, p. 721). I have to state that I have had the same experience and treated the cases the same way. But I have observed that shock only occurred when the injection was given in the deltoid muscle. It did not occur in the same person when given in the buttock. Every person mentioned in this article had injections in the deltoid muscle. I have observed the same reaction with liver extract. The sudden and intense pain may precipitate this condition.

### Numbering of Toes

Dr. WILFRED HUDSON (Banbury) writes: Dr. Walter Addey's letter (*Journal*, October 29, p. 1089) in which he advocates that the toes should be designated "big, index, middle, ring, and little" is so outrageous that I feel a counter-suggestion would not be out of place, especially as it would "leave no room for doubt as to which is meant," and would be readily understood by all age groups in the English-speaking world. Why not "market, home, roast-beef, none, and wee-wee-wee"?

### Breath-holding Attacks

Dr. W. C. HOLLEY (West Wallsend, N.S.W., Australia) writes: The treatment of breath-holding is not difficult, as is stated in the leading article (*Journal*, August 13, p. 422). As soon as the child looks like having an attack, a cold-water tap is turned full on and the child's head held under the running water until the attack stops. After a few of these treatments the child will inhibit the attack as soon as it hears the running water and will later stop the attacks completely. Whether this damages the child's ego I do not know, but it certainly stops the attacks.

# Obituary

## SETON PRINGLE, O.B.E., M.Ch., F.R.C.S.I.

We record with regret the death on November 11 of Mr. Seton Pringle, a past President of the Royal College of Surgeons in Ireland, after a long and trying illness. He was 76 years of age.

Born at Clones, Co. Monaghan, on July 6, 1879, Seton Sidney Pringle left Campbell College, Belfast, in 1897 to enter the School of Physic at Trinity College, Dublin, where his course was a brilliant one. He won the Hutchinson Stewart Scholarship and the then newly founded Fitz-Patrick Scholarship, awarded to the student obtaining the highest aggregate of marks in all examinations throughout his course from the first to the final M.B. He took his B.A. in 1902, and the degrees of M.B., B.Ch. in the following year. In 1905 he became a Fellow of the Royal College of Surgeons in Ireland.

[*Lafayette*

Appointed in 1904 to the surgical staff of Mercer's Hospital, he had as senior colleagues there the late R. C. B. Maunsell and the ebullient "Billy" Wheeler, who were steadily making Mercer's reputation as a centre for good surgical teaching. In Dublin, the home of the first "voluntary" hospital foundations in the United Kingdom, a student, by tradition, enrolled at one of the city's teaching hospitals, and was free to attend all; and the surgical clinics at Mercer's in the early years of the present century were second to none in attraction. Between 1905 and 1918 Pringle's reputation as a sound rather than a showy teacher at the bedside steadily grew. In those years he had also been an examiner for the F.R.C.S.I. and at Trinity College. As an examiner he was pleasant and factual, seeking to assess what the candidate knew rather than what he did not know. Shortly after the outbreak of the first world war in 1914 Dublin Castle became a Red Cross hospital, and Pringle, as a lieutenant-colonel in the R.A.M.C., was a very active member of the staff. Subsequently he was commanding officer of the Irish Counties War Hospital from 1917 to 1919. He was appointed O.B.E. for his war services.

In 1918 Pringle left Mercer's to join the staff of the Royal City of Dublin Hospital at Baggot Street, and there his reputation as an operator grew rapidly, particularly in the field of abdominal surgery. Within the next few years he was appointed consulting surgeon to the Drumcondra, Rotunda, and Royal Victoria Eye and Ear Hospitals. In 1925 he was appointed by the board of Trinity College to be special lecturer in surgical pathology, which appointment was described in *Dublin University Calendar* as "for the present holder only." In 1936 the University conferred upon him the M.Ch. Pringle was President of the Royal College of Surgeons in Ireland from 1934 to 1936, and of the Royal Academy of Medicine in Ireland from 1940 to 1942.

We are indebted to Mr. WILLIAM DOOLIN for the following appreciation: It is a little difficult to recall details of

the professional activity of a colleague who had retired voluntarily from practice some ten or eleven years ago. That retirement had come as a surprise to all who were accustomed to meet Seton Pringle in the full vigour of his activity, whether on the council of the Royal College of Surgeons in Ireland or at the weekly meetings of the Biological Club—familiarly known as "The Bi"—or at meetings of the Section of Surgery of the Royal Academy of Medicine in Ireland. In any company he had been a striking figure, tall, handsome, and spare of build. Erect of carriage and quick of movement, it seemed impossible to believe that he had reached the age which he had always set for his retirement: he looked twenty years younger than the 65 to which he then confessed.

Looking back, one's chief impression is that Pringle was a "man of his hands." His theatre technique was impeccable. Coming early under the influence of Berkeley Moynihan at Leeds, he applied in his own work all that he had learned from that master surgeon. To watch him carry out a difficult cholecystectomy or a colectomy was to see Moynihan's technique put into practice. Pringle did not have Moynihan's gift of speech: once he confessed that he had never really cared for lecturing, though he would sorely miss the theatre. Pressed again and again for a contribution to the *Journal of the Royal Academy of Medicine in Ireland*, he would plead that "writing was an awful bother" to him. Going back now over the files of that journal, one realizes that he wrote little, but what little he did write was like his lectures, sound, matter-of-fact, and without frills. His chief interest for many years was in the surgery of the colon: his concern to lower the mortality rate for intestinal anastomosis in those years when antibiotics were as yet undreamt of is manifest in two notable contributions to the *British Journal of Surgery* in 1924 and 1940. In 1925, in the same journal, he reported the first successful enucleation of a pancreatic cyst performed in Dublin. His last contribution was to the *Irish Journal of Medical Science* in 1940, in which he recorded a three-stage resection of the rectum and lower pelvic colon for an extensive rectal stricture due to lymphogranuloma inguinale, with preservation of the anal sphincter and avoidance of a permanent colostomy.

His recreations were simple: a countryman born and bred, he was a good man with rod and gun. He was a most thoughtful host. I recall with pleasure an invitation to dine with him shortly after his remarriage. Early in the afternoon of the appointed day came a telephone call: "I have three good wines for to-night" (naming three excellent Burgundies). "Which of them would you like me to put out for dinner?" He was crediting his guest with an expertise to which the latter could lay no claim, but the party was as good as the wine.

His first wife, who was the daughter of Dr. Andrew M'Munn, of Ballymote, died in 1938. They had three sons —one of whom is now professor of surgery at the Royal College of Surgeons in Ireland—and two daughters. His second wife, formerly Miss Eileen Blandford, of Dublin, is to-day president of the Council of the St. John Ambulance Brigade, Ireland, in which office she had succeeded her husband. In 1944, on his retirement from practice, they went to live on his farm at Kilmessan, Co. Meath, situated over the little river hard by Bective Abbey. Here he was yet to enjoy ten happy and active years, delighting, on the rare occasions when I met him in town, still the "man of his hands," to tell of the palings he was erecting, or of the growth of the saplings he had planted with his own hand.

## WILLIAM MACKENZIE, M.D., F.R.C.S.Ed., D.P.H.

Dr. William Mackenzie, long and honourably associated with the care of crippled children in Northumberland and Newcastle-upon-Tyne, died suddenly on October 25 at the age of 77. For many years he had been medical superintendent of the W. J. Sanderson Orthopaedic Hospital School for Children at Gosforth.

William Mackenzie was born on September 27, 1878, the son of James Mackenzie, of Torr House, Elgin, and his youth was spent in Edinburgh. From George Watson's College he went on to study medicine at Edinburgh University, where he graduated M.A. in 1899, B.Sc. with distinction in 1902, and M.B., Ch.B. in 1903. After a period as house-surgeon at the Seamen's Hospital, Greenwich, and a course of midwifery at the Rotunda Hospital, Dublin, where he became a close friend of the late Sir Napier Burnett, he returned to Edinburgh for further study, obtaining the F.R.C.S.Ed. in 1905 and proceeding to the M.D. with commendation in 1906. Burnett had suggested to him that Gosforth, a pleasant and growing suburb north of Newcastle-upon-Tyne, might be a promising locality in which to start a practice, and, acting on this advice, Mackenzie put up his plate there in 1907. A year later he was appointed honorary assistant surgeon to the Fleming Memorial Hospital, now the Hospital for Sick Children, Newcastle-upon-Tyne, and he held this appointment, which gave him a valuable opportunity to acquire dexterity in orthopaedic surgery, for the next six years. He was also asked to take medical charge in an honorary capacity of a home for crippled children founded by W. J. Sanderson, but at that time this home had no facilities for surgical treatment. These two appointments at this early stage of his career set the lines on which the main interest of his life developed. In 1912 he added the D.P.H. of Durham University to his long list of qualifications.

During the first world war Mackenzie served for a time in France at the 58th Scottish General Hospital. His service was interrupted by an attack of trench fever with nephritis, and he was invalided home. On recovery he was posted to the Alder Hey Hospital, Liverpool, at that time in use as a military hospital. There his devotion to orthopaedic surgery was further stimulated by the great privilege of working with Sir Robert Jones. After the war he returned to general practice, but more and more of his time was devoted to the care of crippled children. The Sanderson Home became the W. J. Sanderson School for Crippled Children, and eventually expanded into a modern hospital of 141 beds, with an up-to-date operating theatre, *x*-ray plant, and other departments. He was now medical superintendent and orthopaedic surgeon with visiting consultants to help him and with a staff of teachers to carry on the education of the children.

A further development was the establishment of orthopaedic clinics under his charge in Newcastle and in various centres in Northumberland. At these clinics he was able to keep in touch with his own patients and to select suitable cases for admission to the hospital school. Though the credit for the gradual development of this co-ordinated scheme is shared by many people, professional and lay, it was perhaps never fully recognized how much of the new organization was due to Mackenzie's foresight, his knowledge of what was being done in other centres, and his quiet persistent striving for better things. Among the surgeons associated with him in the work of the hospital at different times were the late Professor Rutherford Morison, the late Mr. Hamilton Drummond, and Mr. John Gilmour. Morison and Mackenzie published in 1926 a paper describing what was at that time a revolutionary treatment of "dangle foot," by fixing the ankle-joint by periosteal flaps between the astragalus and os calcis and the lower

ends of the tibia and fibula. The method was afterwards used with success in fixing the knee-joint and the spine. Mackenzie's contributions to the literature of his specialty were not very numerous, but each displayed his powers of acute observation, his scrupulous care in recording case histories, his widespread acquaintance with the relevant literature, and his characteristic humility and diffidence. Among his papers were one on torticollis and another on destructive arthritis in children, both published in the *Newcastle Medical Journal*; and an important more recent paper on painful non-suppurative localized sclerosis of the long bones appeared in the *Journal of Bone and Joint Surgery* in 1947.

During the second world war the Sanderson Hospital was used as a military hospital with Mackenzie as medical superintendent. The children were moved to a place some miles further from the coast, but remained under his care. It was a great grief to him when, with the introduction of the new Health Service, he was superannuated from his post at the hospital which had been the centre of his life's work. He continued, however, to see a few private patients, and was still in harness when the end came. He was a man of few hobbies. In his youth he had been a proficient golfer, but this recreation was denied him by the onset of a unilateral cataract, probably initiated by an accidental blow received during his service in France. He had a great love for old books and for literature in general, and his knowledge of the literary by-ways of the eighteenth and early nineteenth centuries was quite exceptional.

In 1914 he married Miss Margaret Milligan, daughter of the late James Milligan, of Hayfield, Dumfries. The sympathy of a large circle of friends and patients will go out to his devoted wife and two daughters, who had provided for him the inestimable felicity of a happy home.—A. McR.

We are indebted to Professor F. J. NATTRASS for the following appreciation:

I should like to add a few words in tribute to the memory of William Mackenzie. His professional life was of a sort now disappearing, for he combined general practice with the care of children in an orthopaedic hospital. He was not, I think, greatly concerned with operative work, but he had a deep knowledge of bone and joint diseases of childhood, of the treatment of deformities, and of the rehabilitation of children after injuries and operations. To the Sanderson Orthopaedic Hospital, near which he practised, he gave most devoted service for many years, and was largely responsible for the selection of cases for admission there through the orthopaedic clinics of the Northumberland County Council, for the general medical care of the patients, and for a considerable part of their specialist treatment. I knew something of this work, but I knew him better as a general practitioner. I think of him as a doctor of unusually wide knowledge and culture, and with the highest professional standards, and as a man of great charm and great integrity. Scrupulous to a degree in his study and recording of cases, he was not to be hurried, but his earnestness made one forgive the time which might be given to a discussion of a case or a problem. As would be expected of such a man, he was till his last days a constant supporter of medical societies, and on several occasions read papers and showed cases; his papers to orthopaedic journals dealt with some unusual problems and were remarkable contributions from a man in the active life of practice. William Mackenzie had a wonderfully happy home life, was deeply respected by his colleagues and beloved of his patients, and will be greatly missed.

## HANS FINSTERER, M.D.

We are indebted to Sir GORDON GORDON-TAYLOR for the following appreciation:

Perhaps a brief space may be allotted me to pay a tribute to Hans Finsterer, whose death on November 4 was recorded in the columns of the *British Medical Journal* (November 19, p. 1274), for his passing has removed from the world of surgery an international figure. Despite the lack of a large hospital clinic during the peak period of his surgical activity he enjoyed a reputation comparable with that of his Viennese contemporaries von Eiselsberg, Denk, or Böhler, and the very contrast of his surgical environment situated in the Franz Josef Ambulatorium—a private clinic where Finsterer himself paid for the maintenance of the many poor admitted for operation out of the money that he extracted from the rich—may have proved an added attraction to the many surgeons from diverse lands and to the numerous British surgical travelling clubs who visited him. Here was no exhibition of organized team-work; the man was a lone worker, a man with a mission, a mission to promulgate by his own singular results the advantages of a particular method of anaesthesia, which all who cared to use might enjoy. No hordes of surgical acolytes were there to assist him; perhaps the resident doctor of the Ambulatorium or a chance visitor. Some who read these lines may remember the attractive blonde *Schwester* with the gold incisor tooth who presided at the instrument table and who kept the key of the drug and anaesthetic cupboard in her bosom, into which the hand of Franz, the handyman of many duties, had occasionally to dive under her frock in time of emergency and then be withdrawn complete with furtive key to be demonstrated to a smiling audience.

When first I visited him in the early 'twenties there was no blood transfusion: gas-and-oxygen was not only too expensive but was also in short supply. Finsterer was no supreme technician; he was the devotee of regional anaesthesia and of the solar-plexus block by the Braun approach; none were admitted under his care for laparotomy who demanded general narcosis, although of course his intense humanity never denied an ether *Rausch*, probably administered by Franz the porter, to any whose pain during operation was unrelieved by further instillations of local analgesic.

The indubitable value of regional and splanchnic anaesthesia in reducing the mortality of gastrectomy and other operations on the alimentary tract has waned since the consummate advances in anaesthesiology taking place in the years succeeding the termination of the second world war, advances in which British workers have played so notable a part.

Finsterer graduated slowly towards the Billroth I or the Haberer type of anastomosis after gastric resection, employing this technique in patients in whom local anatomical conditions were favourable and the general state good; but from 1932 to 1950 his mortality (2.4%) was even slightly less than in patients operated on by the Hofmeister–Finsterer technique. His exclusion-resection operation for non-resectable duodenal ulcer has long proved valuable in at least my own hands, even in days before Plenk's removal of the mucosa of the pyloric antrum was superadded, and might often be utilized with advantage, particularly to the patient, in days when the yardstick of surgical technical efficiency appears to be the operator's prowess in resecting the first part of an ulcerated duodenum. The number of non-resectable ulcers of the duodenum diminishes with surgical experience, and in one paper Finsterer says that "no ulcer is non-resectable": perhaps he had learned the wisdom of resecting scars rather than burgeoning ulcers of the duodenum.

Methods of anaesthesia and of operative technique have their vogue in the promotion of safe surgery, and probably Finsterer's greatest claim to remembrance will be his contribution to the treatment of ulcer haemorrhage from stomach or duodenum by means of surgery, his early work in this field taking place in the first years of the third decade

of this century, when some surgeons in this country were also endeavouring to shake the physicians out of their contumacious self-satisfaction with the results of medical treatment of the condition despite the evidence of the post-mortem room with the open mouths of arteries in the base of ulcer craters. The fight for early surgical consultation has now been won, and fraternal medico-chirurgical co-operation is now established practice, but it was Finsterer more than any man who pointed out the importance of early operation if success were to be attained. He was frankly Anglophile and had visited Britain on several occasions, including participation in the Nottingham meeting of the B.M.A. The Continental surgeons of the nineteen-twenties were ahead of their British contemporaries with their radical treatment of duodenal ulcer, and Finsterer had almost to be restrained from leaving the operating theatre of one British surgeon who performed a gastro-jejunostomy in his presence; but he exhibited the liveliest satisfaction at watching Grey Turner perform three perineal secretions of the rectum by the Hochenegg technique, for had he himself not been an assistant to the Hofrath in the second surgical clinic in Vienna? He loyally preferred Salzburg to the beautiful Castle Rock in Edinburgh: he contemned the more luxurious restaurants in London, preferring at all times the schnitzel in the eating-houses of Charlotte Street. In the old days of the Ambulatorium he lunched off a roll taken out of his pocket, a lunch almost as frugal as Grey Turner's brew of strong tea and a boiled egg taken between operations at the Royal Victoria Infirmary, Newcastle.

I saw Finsterer at Frankfurt in 1950, when he walked some miles to see me and was unfeignedly pleased to meet me again after the war. In 1952 in Munich he had obviously aged, and the sap of life ran more dry; but the kindliness that had always been his remained. He cared nothing for politics, recking little of changes, yet glad when a municipal hospital fell his way, for it gave him increased facilities for surgical work. But I believe that his zenith was in the environment of the Ambulatorium, when, single-handed, he conducted a surgical mission and promulgated a gospel which is not outmoded to-day.

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Dr. ARCHIBALD DODD died suddenly at his home at Kirkham, Lancashire, on October 20 at the age of 51. Born on March 14, 1904, and educated at St. Helens, where his father was later mayor, and at Liverpool University, Archibald Dodd graduated M.B., Ch.B., with honours, in 1927, and took the London Conjoint diploma in the following year. After experience in hospital and as a ship surgeon, he went into general practice at Manchester and later at Liverpool, but gave it up for health reasons and decided to enter the public health service. He took the Liverpool D.P.H., with a distinction, in 1937, and proceeded to the M.D. a year later. Public health appointments at Birkenhead and Dewsbury followed, and then he entered the service of the Lancashire County Council, in which, after promotion to the post of divisional medical officer for the Fylde division, he stayed until his retirement owing to ill-health early this year. During the second world war Dr. Dodd served in the R.A.M.C. from 1942 to 1946 as a hygiene specialist, and on leaving the Army was granted the honorary rank of lieutenant-colonel.

E. D. I. and J. W. P. write: Archie Dodd was big of frame and generous of heart; we who knew him well from his early student days enjoyed his friendship and jovial company. He was sympathetic with the less fortunate, and, as might be expected of one with such an open and gifted nature, he soon gained the confidence and affection of all with whom he was associated. He loved the country and country pursuits, and found much that was congenial to him in his Lancashire appointment. Ill-health had rather dogged him, but he had few other worries. Our sympathies go out to his widow and daughter.

Dr. R. E. CREE died at Beaminster, Dorset, where he had been living in retirement, on October 24 at the age of 77. Robert Ewart Cree was born at Dublin on December 7, 1877, the youngest son of Mr. George Cree, barrister-at-law, and was educated at St. Stephen's School and at Trinity College, Dublin. He graduated B.A. from Dublin University in 1898, and three years later obtained the degrees of M.B., B Ch. He proceeded to the M.D. in 1902, in which year he also took the B.A.O. and the L.M. after completing the course at the Rotunda Hospital. He served in the South African War, being awarded the Queen's medal. After the war he continued his studies at Vienna, Freiburg, Heidelberg, and London before setting up in practice as an ophthalmic surgeon at Newcastle-upon-Tyne. On the outbreak of the first world war in 1914 he entered the R.A.M.C. and served in France with the 6th Cavalry Field Ambulance, and was awarded the Military Cross in 1916 for outstanding bravery in evacuating wounded while under heavy shell-fire. He later served in Mesopotamia, Italy, Salonika, and the Caucasus. Invalided home in 1919, he resumed his ophthalmic practice at Newcastle and was appointed consulting ophthalmic surgeon to the Fleming Memorial Hospital and to the Ministry of Pensions clinics. In 1928 he moved to London, continuing his work for the Ministry of Pensions and taking up general practice at Willesden, where he made full use of his skill in ophthalmology. During the second world war he worked at the Ministry of Pensions Hospital at Llandrindod Wells, becoming deputy medical superintendent. He returned to Willesden in 1945 and continued in practice there until a few months ago, when progressive illness compelled his retirement and he went to live at Beaminster. His death will be mourned by the many patients to whom he had endeared himself and by his former colleagues. He is survived by his widow and a son, to whom our sincere sympathy is extended.

M. M. writes: By the death of Dr. R. E. Cree there has been removed from the medical scene a gallant and cultured physician of the last generation. Doctor, soldier, athlete, musician, and lover of fine things, he brought to bear upon every facet of his long and varied career on the one hand outstanding courage and determination, and on the other the impact of a lively and cultivated mind. He spent his youth in the atmosphere of charm and graciousness which was the Dublin of the late nineteenth century. His father's house was a hub of musical Dublin, and Cree himself studied the 'cello from the age of 7. He became a very accomplished 'cellist, winning many awards and gold medals, and he would recall with nostalgia the many fine musical occasions in which he took part at his house. Of short stature, he was nevertheless an outstanding athlete at Trinity, and characteristically chose that branch of athletics which perhaps more than any other calls for grit and determination—long-distance running. He acquired the nickname and repute of "a pocket Hercules," and some of his records stood for many years. To the end of his life he retained his fine clinical acumen and his lively and experimental approach to therapeutics, and earned the respect of his colleagues, both general practitioners and consultants.

Dr. HERMAN WOLFE, who had practised in Otley for 40 years, died suddenly on November 1 at the age of 76. He was a native of Sunderland, where his ancestors had lived for over two hundred years. At Durham University, where he studied medicine, he won the Dickinson scholarship in 1903 and graduated M.B., B.S. in the following year. He proceeded to the M.D. in 1908. Though engaged in a busy general practice, he studied for and gained the D.P.H. of Leeds University in 1920. After qualification he became a house-surgeon at the Royal Infirmary, Bradford, where he remained for about two years, holding various resident appointments. He then gained wide experience as a locumtenent in a number of practices in the north of England. In 1912 he came to Otley as a locum, but he decided to remain there and soon became a principal in an established medical practice. For nearly thirty years he was medical officer of

health for the Wharfedale Rural District, and in 1938 he was appointed medical officer of health for the Otley Urban District. When the health services were reorganized in 1947 he relinquished both these appointments. For thirty years he was police surgeon at Otley, and he was also medical officer to the Brampton branch of the National Children's Homes, being chairman of the committee of management for eight years. During the second world war he was responsible for the whole of the first-aid services in Otley and Wharfedale. In 1916 he married Theodora, only daughter of the late Sir James Hastings Duncan, the then Liberal Member of Parliament for the Otley Division. They had two sons.

Dr. C. VERNON LIGHT writes: Dr. Hermon Wolfe was known to almost everyone in Otley and Wharfedale, not only because he was an outstanding general practitioner, but because he was kind, conscientious, patient, and painstaking. A sound clinician, he was a regular attender at meetings of the West Riding Medico-Chirurgical Society, and he regarded it as a great honour when he was elected president of the society in 1944. He was a prolific reader, and his knowledge of Shakespeare was profound. Keenly interested in sport, he had begun his eighth year as president of the Otley Rugby Union football club shortly before his death, and had been honorary surgeon to the club for over thirty years. In his work he possessed astonishing drive and tenacity of purpose. Punctuality was another of his many attributes, and winter and summer alike, and through that period of the war when the countryside was cloaked in deepest "blackout," he drove his car around difficult Yorkshire moorland country in ice and fog and snow. It was with great regret that we learned he had decided to retire from general practice after 40 years of devoted service. But he continued as a friend regularly to call upon his elderly patients, rich and poor alike, and his visits were anticipated with sincere pleasure by all. He was president of the Otley Old Folk's Association, and worked hard for that body until his sudden death. To his family, his widow, and his sons our heartfelt sympathy is extended.

Dr. T. M. CRAWFORD died on November 2 at Willenhall, Staffordshire, where he had been in practice for the past 38 years. He was 71 years old. Thomas Maitland Crawford was one of nine sons of the late Sir Thomas Crawford, formerly Director-General of the Army Medical Services, and honorary surgeon to Queen Victoria. One of his two sisters was a former matron of St. Thomas's Hospital. After graduating B.A. at Trinity College, Dublin, he took the Scottish triple qualification in 1912, and subsequently served for a time as a ship surgeon with the Canadian Pacific Steamship Company. At the outbreak of hostilities in 1914 he joined the R.A.M.C. and served throughout the war, being awarded the Military Cross in 1917 for conspicuous gallantry under fire. Dr. Crawford's family have a distinguished record, and in all he and his brothers were awarded four M.C.s, two D.S.O.s, one O.B.E., and one mention in dispatches. Three of the family received their decorations at the same investiture. In addition the late Dr. Hugh Crawford, O.B.E., was a well-known figure in the Boy Scout movement and was awarded the Silver Wolf. After demobilization Dr. T. M. Crawford was appointed resident medical officer at New Cross Hospital, Wolverhampton, and subsequently entered general practice at Willenhall, where he was the senior practitioner at the time of his death. He built up a large and extensive practice and was devoted to the care of his patients, and his numerous good deeds and acts of friendliness will long be remembered by his patients. His professional colleagues greatly admired his clinical acumen and judgment, which was of the highest order. During his last illness Dr. Crawford showed great courage and conducted his evening surgery until a week or so before his death. He had an extremely happy married life, and the high esteem in which he was held by all will bring some measure of consolation to his widow.—J. E. S. L.

Captain A. N. CAHUSAC, O.B.E., *M.C.*, who died on November 14, was appointed chief secretary of the St. John Ambulance Association in 1918. He retired from this post in September, 1953, after 35 years' service. He was known to many people throughout the world as a courteous and kindly adviser in all matters pertaining to first aid, home nursing, and kindred subjects, and he had an exceptional fund of knowledge built up by personal experience over the years. He was chairman of many revision committees of the textbooks published by the St. John Ambulance Association, and was also the editor of most of the new publications brought out by the association during the time that he was chief secretary. The service he gave to the St. John Ambulance Association will be remembered for many years to come.

# Medico-Legal

## HOUSE-SURGEON'S DUTY

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On February 8, 1951, William Alexander Macdonald, a bank accountant aged 47, was admitted to Killearn Hospital, Stirlingshire, for an operation for a minor foot complaint, which was successfully carried out. He was making a good recovery, but complained of feeling sick. A sedative relieved his symptoms.

On February 12 Dr. James Brown, the house-surgeon, examined him, and he complained of being sick and of slight abdominal discomfort. Dr. Brown reported the matter to the consulting surgeon and the senior registrar, who both examined the patient and indicated that there was very little wrong, but told Dr. Brown to keep an eye on him. Dr. Brown examined the patient on the morning of February 13, and found no abnormality. He did not see the patient again until 7 p.m. on the evening of February 14, a day on which the patient had been visited by his wife, who was shocked to see how ill he was looking. Dr. Brown examined him and came to the conclusion that he was not suffering from abdominal obstruction. He saw him again later that evening and on the morning of February 15. Later that day the ward sister reported to Dr. Brown in the theatre that the patient had collapsed and was vomiting. He was removed to Glasgow Infirmary and an operation was performed for intestinal obstruction, but he died there the next morning.

On November 11, 1955,[1] Lord Strachan in the Court of Sessions awarded his widow £4,400 and his two children a total of £1,250 damages in an action brought against Dr. Brown and the Glasgow Western Hospital Board of Management for negligence. Mrs. Macdonald's case was that Dr. Brown was negligent in failing to diagnose the obstruction, and the Board was vicariously liable for his negligence. In his judgment Lord Strachan said that he could not hold on the evidence that a house-surgeon using ordinary care would or should have diagnosed an intestinal obstruction on February 14. But as regards his failure to report to his seniors on that date the position was different. If a doctor of limited experience, such as an ordinary house-surgeon, suspected a condition which would almost certainly endanger life unless attended to immediately, it was clearly his duty to refer the case to someone who had the necessary experience to deal with it. To refrain from doing so was a failure to take reasonable or ordinary care for the life of the patient. Dr. Brown ought to have reported to his seniors on February 14. The reasonable probability which arose on the evidence was that, if he had, Mr. Macdonald's life would have been saved.

The liability for damages and costs was by agreement divided equally between Dr. Brown and the Board.

The Medical and Dental Defence Union of Scotland acted for Dr. Brown.

[1] *Scotsman, November* 5, 6, and 12, 1955.

# Medical Notes in Parliament

### Amalgamation of Armed Forces Medical Services

The Minister of Defence was asked by Colonel M. STODDART-SCOTT (Ripon, Con.) on November 16 if, to save medical manpower and public money, he would consider amalgamating the medical services in the three fighting Services and form one defence medical service. Mr. SELWYN LLOYD stated that the amalgamation of the medical services of the armed Forces was rejected by the Government of the day early in 1948. It was one of the matters that had been examined by the committee under Lord Waverley on the medical and dental services of the Forces. Their report was now being considered, and he would announce in due course the Government's decision.

### Fluoridation Experiments

Captain H. KERBY (Arundel and Shoreham, Con.) asked the Minister of Health how many experimental centres were in existence in England and Wales, and how many were planned, for research into the effects of fluoridation of public water supplies upon humans and animals. Mr. MACLEOD stated that four local authorities in England and Wales and one in Scotland were planning to demonstrate the benefits of fluoridation of public water supplies in reducing the incidence of caries in teeth.

Mr. D. WADE (Huddersfield, West, Lib.) asked the Minister whether he would arrange that no further experiments be carried out in the fluoridation of water without the approval of users who had no other source of supply. Mr. MACLEOD declined, stating that it was for local authorities themselves to decide whether they wished to take part in these studies.

### Tuberculosis in Malaya

Mr. R. SORENSEN (Leyton, Lab.) asked the Secretary of State for the Colonies what further steps the Government of the Federation of Malaya had taken to combat tuberculosis; and why treatment allowances had been refused despite the results achieved by the scheme in Singapore. Mr. A. LENNOX-BOYD stated on November 16 that, in addition to a major campaign against tuberculosis during the past five years, the Government of the Federation of Malaya had this year given $300,000 to the Lady Templer Tuberculosis Hospital and had also improved facilities at eight Government tuberculosis centres. The Federation Government had been unable to adopt a country-wide scheme of treatment allowances owing to the large and scattered population, and the resulting cost involved and difficulties of supervision, but a voluntary scheme of allowances was administered by the Malayan Association for the Prevention of Tuberculosis.

### Expenditure on Food

Sir EDWARD BOYLE, Economic Secretary to the Treasury, stated in answer to Mr. E. FERNYHOUGH (Jarrow, Lab.) on November 17 that between the second quarter of 1951 and the second quarter of 1955, the latest for which figures were available, consumers' expenditure on food was estimated to have increased from £739m. to £1,032m., or by 40%. The increase in volume of consumption was about 9%, while prices rose about 28%.

### Agene Ban

Mr. N. DODDS (Erith and Crayford, Lab.) asked on what date the ban on the use of agene in food became operative; and what precautions would be taken to ensure that nitrogen trichloride was not used in some other form in breadmaking. Mr. AMORY replied that arrangements made by the flour millers and flour importers provided for nitrogen trichloride in any form to cease to be used in flour by the end of this year.

### Measurements of Air Pollution

Mr. J. R. BEVINS, Parliamentary Secretary to the Ministry of Works, supplied on November 15 at the request of Mr. G. NABARRO (Kidderminster, Con.) the extent and degree of atmospheric pollution in the 30 most heavily polluted local authority areas. He stated that measurements were made by the local authorities in co-operation with the Department of Scientific and Industrial Research in 333 areas, mostly where pollution was high. The details are:

*Insoluble Deposited Matter in 30 Selected Local Authorities Area: Annual Average 1949–54*

| Site | Weight (in grammes) of insoluble matter which falls on an area of 100 sq. metres each month |
|---|---|
| Rawmarsh (Parkgate, Granby House) | 3,800 |
| Billingham (Belasis Avenue) | 3,530 |
| Southwark (Bankside, Greenmore Wharf) | 2,990 |
| Wellingborough (Finedon Road) | 2,450 |
| Eston (Grangetown, Cleveland House) | 2,220 |
| Kearley (Weir) | 2,060 |
| Derby (Osmaston) | 1,940 |
| Stretford (Trafford Park) | 1,860 |
| Bradford (Sugden Street) | 1,710 |
| Port Talbot (Taibach, Regent Cinema) | 1,620 |
| Doncaster R.D. (Askern Vicarage) | 1,550 |
| Stockport (Portwood) | 1,490 |
| Willesden (Minet Gardens) | 1,430 |
| Leeds (Burley Park) | 1,240 |
| Manchester (Phillips Park) | 1,220 |
| Greenwich (Fuel Research Station) | 1,220 |
| Battersea (Battersea Park) | 1,180 |
| Bilston (Dudley Street) | 1,120 |
| Bristol (Portishead Dock) | 1,040 |
| Stocksbridge (Town centre) | 1,020 |
| Middlesbrough (South Bank Road) | 1,010 |
| Hornsey (Raleigh Road, West) | 1,010 |
| Rotherham (Blackburn) | 1,010 |
| Sheffield (Attercliffe) | 1,000 |
| Croydon (Barracks) | 960 |
| Bootle (Litherland Road) | 940 |
| Smethwick (Gasworks) | 900 |
| Bolton (Police Sports Ground) | 900 |
| Birmingham (Great Charles Street) | 880 |
| Salford (Ladywell Hospital) | 860 |

*Sulphur Dioxide by the Volumetric Method in 30 Selected Local Authorities Areas: Annual Average 1949–54*

| Site | Concentration of sulphur dioxide in the air (parts per 100 million) |
|---|---|
| Leeds (Market Buildings) | 16 |
| Salford (Regent Road) | 15 |
| Lambeth (County Hall) | 14 |
| Sheffield (Surrey Street) | 14 |
| Westminster (Monck Street) | 13 |
| Woolwich (Beckton) | 12 |
| Bradford (Town Hall) | 11 |
| City of London (Golden Lane) | 11 |
| Wakefield (Northgate) | 11 |
| Bolton (Civic Centre) | 10 |
| Leicester (Greyfriars) | 10 |
| Southwark (Walworth Road) | 10 |
| Manchester (Rusholme) | 10 |
| Twickenham (National Physical Laboratory) | 10 |
| Glasgow (Central) | 9 |
| Newcastle-upon-Tyne (Dean Street) | 9 |
| Warrington (Sankey Street) | 9 |
| Greenwich (Fuel Research Station) | 8 |
| Preston (Lancaster Road) | 8 |
| Birmingham (St. Martin's Street) | 7 |
| Burnley (Parker Lane) | 7 |
| Stocksbridge (Town Centre) | 7 |
| Bilston (Wellington Road) | 6 |
| Leyton (Sidmouth Road) | 6 |
| Chiswick (Town Hall) | 5 |
| Hornchurch (Billet Lane) | 5 |
| Kingston-upon-Hull (High Street) | 5 |
| Brierley Hill (Dudley Road) | 4 |
| Longbenton (N.C.B. Laboratory) | 4 |
| Wolverhampton (Waterloo Road) | 4 |

### Limbless Pensioners' Claim

The Minister of Pensions and National Insurance was pressed on November 4 about the claim submitted by the British Limbless Ex-Servicemen's Association, which Dame IRENE WARD (Tynemouth, Con.) said was supported by the Presidents of the Royal College of Physicians and of the Royal College of Surgeons, other high medical opinion, and the whole of the House. Mr. OSBERT PEAKE replied that the claim had been repeatedly examined by successive Ministers over a long period, and they had all come to the conclusion that it was not possible to treat specially aged limbless persons, and distinguish them from other equally deserving cases of persons suffering equal disability, but who had not lost a limb. To pick out limbless persons as such for some special benefit would be bitterly resented by

other classes of pensioners, such as the paralysed, who would think they were being unfairly treated. Mr. H. MARQUAND (Middlesbrough, East, Lab.) suggested that the Minister should consider modifying the comforts allowance to include in it some element of compensation for age and the effect of war injuries on it. Mr. PEAKE said that he would look at the suggestion.

### Ban on Heroin

Dr. H. M. KING (Itchen, Lab.) asked the Minister of Health on November 21 what reply he had given to recent protests of the medical profession made to him against the proposed banning of the manufacture of heroin. Mr. IAIN MACLEOD said that he did not feel justified in departing from the advice he had given to the Home Secretary, after consulting the Standing Medical Advisory Committee.

# Vital Statistics

### Unexplained Illness at School

At Tottington Secondary Modern School in Lancashire 60 of the 190 children have recently suffered an illness whose aetiology is at present unknown. Dr. C. H. T. Wade, divisional medical officer, is investigating it. The signs and symptoms suggested that the children were affected by a poison attacking the central nervous system. Two of the children became unconscious for a short time and several were semiconscious. Dilatation of pupils, changes of pulse rate, and vomiting were observed. A normal temperature was the rule. The children recovered quickly within a few days. Food has been excluded as a source of the poison, and carbon monoxide is believed not to have been responsible. One possibility being investigated is that fumes from an organic phosphorus insecticide may have been liberated from some sacks used for cleaning. They were stored in a cellar and became warm just before the outbreak because central heating was increased. What is believed to be an exactly similar outbreak recently affected 30 girls in a school at West Hartlepool, County Durham.

### Week Ending November 12

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,011, whooping-cough 1,072, diphtheria 16, measles 2,355, acute pneumonia 442, acute poliomyelitis 226, dysentery 535, paratyphoid fever 12, and typhoid fever 5.

### Infectious Diseases

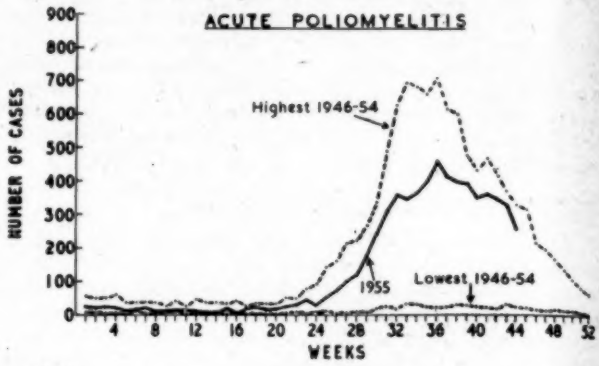
The largest changes in the number of notifications of infectious diseases in England and Wales during the week ending November 5 were decreases of 145 for food-poisoning, from 288 to 143, 102 for scarlet fever, from 888 to 786, and 70 for acute poliomyelitis, from 329 to 259, and increases of 115 for whooping-cough, from 833 to 948, and 26 for measles, from 2,301 to 2,327.

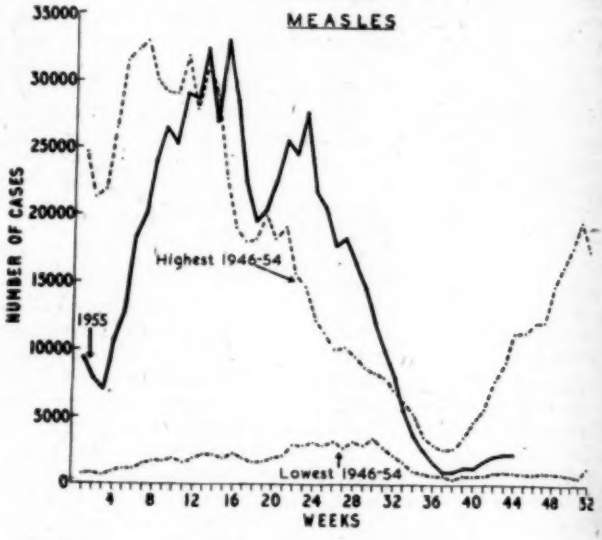
The largest decline in the incidence of scarlet fever was 63 in Yorkshire West Riding, from 163 to 100. The largest rises in the number of notifications of measles were 53 in Devonshire, from 242 to 295, and 40 in Kent, from 42 to 82. The largest increases in the incidence of whooping-cough were 42 in Yorkshire West Riding, from 86 to 128, and 37 in Durham, from 61 to 98. 5 cases of diphtheria were notified, being 6 fewer than in the preceding week; two of these cases were notified in Staffordshire.

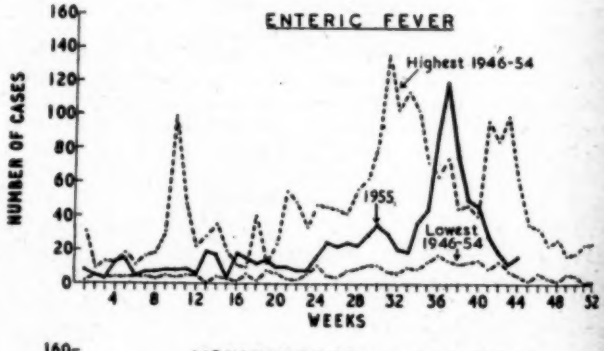
The chief centres of dysentery were Lancashire 107 (Liverpool C.B. 51, Bolton C.B. 12, Oldham C.B. 9), Yorkshire West Riding 80 (Leeds C.B. 37, Huddersfield C.B. 19), London 42 (scattered among 15 boroughs), Lincolnshire 39 (Boston R.D. 39), Middlesex 27, and Warwickshire 23 (Birmingham C.B. 10).

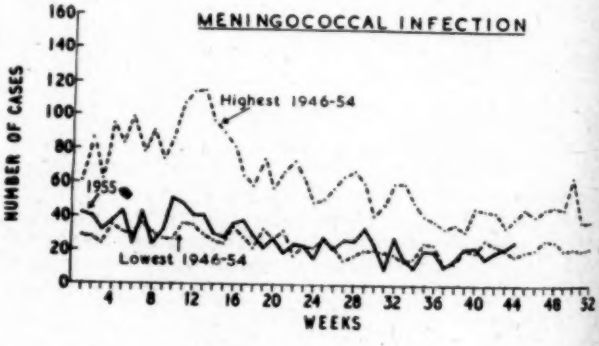
### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 5** (No. 44) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

| CASES in Countries and London | 1955 | | | | | 1954 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire | Eire |
| Diphtheria | 5 | 1 | 6 | 0 | 1 | 14 | 1 | 5 | 0 | |
| Dysentery | 482 | 42 | 146 | 13 | | 468 | 38 | 210 | 3 | 1 |
| Encephalitis, acute | 2 | 1 | | 0 | | 3 | 0 | | 0 | |
| Enteric fever: Typhoid | 5 | 0 | 1 | 1 | 2 | 2 | 0 | 0 | 0 | 2 |
| Paratyphoid | 11 | 1 | 1 | 0 | | 14 | 0 | 11 (B) | 0 | |
| Food-poisoning | 143 | 19 | | 1 | | 164 | 11 | | 2 | |
| Infective enteritis or diarrhoea under 2 years | | | | 19 | 35 | | | | 13 | 13 |
| Measles* | 2,327 | 28 | 39 | 17 | 35 | 4,635 | 285 | 572 | 167 | 73 |
| Meningococcal infection | 26 | 2 | 10 | 0 | | 19 | 1 | 14 | 0 | |
| Ophthalmia neonatorum | 31 | 1 | 6 | 0 | | 32 | 3 | 9 | 0 | |
| Pneumonia† | 368 | 20 | 146 | 4 | 1 | 351 | 30 | 143 | 4 | |
| Poliomyelitis, acute: Paralytic | 154 | 20 | 21 | 5 | 7 | 36 | 1 | 26 | 2 | 2 |
| Non-paralytic | 105 | 19 | | | | 23 | 1 | | | |
| Puerperal fever§ | 204 | 30 | 5 | 3 | | 240 | 55 | 13 | 1 | 1 |
| Scarlet fever | 786 | 76 | 100 | 40 | 35 | 636 | 27 | 155 | 36 | 32 |
| Tuberculosis: Respiratory | 621 | 75 | 145 | 20 | | 700 | 82 | 137 | 14 | |
| Non-respiratory | 101 | 5 | 22 | 6 | | 89 | 2 | 17 | 1 | |
| Whooping-cough | 948 | 44 | 70 | 73 | 74 | 1,953 | 98 | 124 | 19 | 33 |

| DEATHS in Great Towns | 1955 | | | | | 1954 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Dysentery | 0 | 0 | | 0 | | 0 | 0 | | 0 | |
| Encephalitis, acute | | 0 | | | 0 | | 0 | | | 0 |
| Enteric fever | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | |
| Infective enteritis or diarrhoea under 2 years | 3 | 0 | 1 | 0 | 0 | 5 | 0 | 0 | 1 | 1 |
| Influenza | 9 | 3 | 0 | 0 | 1 | 9 | 0 | 2 | 0 | 1 |
| Measles | | 0 | 0 | 0 | 0 | | 0 | 1 | 0 | 0 |
| Meningococcal infection | | 0 | 0 | | | | 0 | 0 | | |
| Pneumonia | 240 | 39 | 24 | 10 | 4 | 160 | 16 | 21 | 3 | 8 |
| Poliomyelitis, acute | 9 | 2 | | | 0 | 4 | 0 | | | 1 |
| Scarlet fever | | 1 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |
| Tuberculosis: Respiratory | 78 | 9 | 11 | 0 | 3 | 59 | 6 | 9 | 1 | 7 |
| Non-respiratory | | 0 | 0 | 1 | 1 | | 0 | 10 | 0 | 1 |
| Whooping-cough | 0 | 0 | 0 | 2 | 1 | 3 | 0 | 0 | 0 | 1 |
| Deaths 0–1 year | 195 | 24 | 34 | 7 | 13 | 189 | 22 | 27 | 3 | 6 |
| Deaths (excluding stillbirths) | 5,617 | 840 | 598 | 97 | 190 | 4,810 | 702 | 518 | 88 | 163 |
| **LIVE BIRTHS** | 6,890 | 1044 | 855 | 197 | 498 | 6,701 | 1021 | 794 | 201 | 389 |
| **STILLBIRTHS** | 183 | 25 | 24 | | | 196 | 20 | 23 | | |

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Medical News

**Deputy Vice-Chancellor of London University.**—Dr. C. F. HARRIS, dean of the faculty of medicine, and formerly dean of St. Bartholomew's Hospital Medical School, has been appointed deputy vice-chancellor of the University of London for the remainder of the year 1955–6.

**College of General Practitioners.**—The first annual dinner of the College was held on November 18 in the Hall of the Society of Apothecaries. Dr. WILLIAM PICKLES, who presided, in proposing the health of the guests mentioned those institutions and periodicals which had supported the College in their various ways, and expressed their particular appreciation of the help the College had received from the Master and the Society of Apothecaries. It used to be said, Dr. Pickles observed, that the physician was someone who knew a lot but could do nothing and the surgeon someone who did a lot but knew nothing. But to-day the specialist was the first to appreciate the work done by the general practitioner at the bedside of the patient, and there was a spirit of mutual trust and respect between the two. Dr. Pickles said that the present position of the College showed how well the original steering committee had done its work, and especially welcomed the presence at the dinner of one of its members, Mr. H. U. WILLINK. In response, Mr. DICKSON WRIGHT said he was flattered by the invitation to speak on behalf of so many illustrious guests. His father and grandfather had been in general practice. Mr. Dickson Wright confessed to a failing of forgetting three things: people's faces, people's names—and he forgot what the third was that he could not remember. Sir HENEAGE OGILVIE proposed the health of the College in an urbane and polished speech. In reply Dr. I. D. GRANT said that the College had been founded as an act of faith in British medicine at a time when some were despondent about the future. The College of General Practitioners was essentially a band of altruists. They left the problems of remuneration and conditions of service entirely in the trustworthy hands of the B.M.A. The College was concerned with standards of practice and anxious that general practitioners should be something more than signposts to the nearest hospital, and particularly desirous that students should be taught the rudiments of general practice before entering it. Given the opportunity the College could help the universities in fulfilling that ideal.

**Rockefeller Foundation Grants.**—The keen interest aroused by the recent advances in knowledge of the structure of biologically active proteins is reflected by two Rockefeller grants totalling $700,000 for collaborative work on haemoglobin, myoglobin, and nucleic acids at the Cavendish Laboratory, Cambridge, and the Davy Faraday Research Laboratory of the Royal Institution. Also for research on protein chemistry and metabolism are two analytical ultracentrifuges, costing $25,000 each, which are being presented to the departments of colloid science at Cambridge and of experimental pathology at Birmingham; research at St. Mary's Hospital Medical School on connective tissue proteins and the metabolism of porphyrins is being supported by a grant of $13,000 for costly equipment. These major benefactions are included in the list of Rockefeller Foundation grants for the third quarter of this year. Other notable grants for medical studies outside Britain include a four-year grant totalling $34,000 to the department of preventive and social medicine at the Christian Medical College at Vellore, in India. Here the intention is to develop a course of health education for village communities which could become a part of the ordinary medical curriculum. Another is for a study by Chicago University on the position of negroes in medicine, especially in relation to the need.

**Drummond Fellowships for Research in Nutrition.**—The managing trustees will consider in March, 1956, applications for not more than one Drummond senior fellowship and not more than two Drummond junior fellowships for

research in nutrition. The value of the senior fellowship will be £900 per annum, to which may be added a grant for expenses of research not exceeding £50 per annum. In addition up to £90 may be paid for superannuation. The value of the junior fellowship will be £500 per annum, to which may be added a grant for expenses of research not exceeding £75 per annum. The fellowships will normally be tenable for two years. Full particulars can be obtained from the hon. secretary, Drummond Trust, University College London, Gower Street, W.C.1. Completed application forms must be received not later than January 27, 1956.

**St. John Ambulance Brigade Surgeon's Conference.**—The surgeon's conference was held in London on November 5 and 6 under the chairmanship of the surgeon-in-chief, Major A. C. WHITE KNOX. The programme included talks on "Cancer: Is Cure Worth Mutilation?" (Professor IAN AIRD), medico-legal aspects of first aid (Dr. J. A. GORSKY), and "The Implications of Hydrogen Bomb Attack" (Mr. G. R. STANBURY). Mr. F. A. RICHARDSON lectured on the organization and operational methods of the London Ambulance Service. At the dinner on November 5 Surgeon Vice-Admiral Sir ALEXANDER INGLEBY-MACKENZIE and Professor AIRD were the principal guests.

**British Asthma Association.**—This is an association for sufferers from asthma. Founded in Manchester in 1953, its aims include the promotion of research on the prevention and treatment of asthma; the provision of information on special facilities for the treatment of children, asthma clinics and centres, and recent advances in therapy; publicity to arouse public interest in the problems of asthmatics; and the support of movements to prevent air pollution. Branches have been started in London and the Home Counties, Liverpool, and Leeds. The chairman of the council is Mr. C. HAMBLEN-THOMAS, F.R.C.S., and the vice-presidents include Dr. D. HARLEY and Dr. G. F. WALKER. The hon. secretary is Mr. F. C. BENTLEY, 103, Manley Road, Whalley Range, Manchester, 16.

**List of Approved Names.**—The General Medical Council has issued a new consolidated list of "approved names" for drugs which includes all those selected since 1948. The names are chosen by the British Pharmacopoeia Commission. In the event of a drug being included in the *British Pharmacopoeia* the approved name becomes its official title. Besides the approved name, the list also records chemical and proprietary names for each drug. The list will be useful to those preparing papers for publication in medical journals. Copies of the list may be obtained on application to the secretary, British Pharmacopoeia Commission, 44, Hallam Street, London, W.1.

**Rauwolfia and Depression.**—In a letter to the *Pharmaceutical Journal* (November 12, p. 463) the makers of "tranquilex," a rauwolfia preparation, announce that they are voluntarily withdrawing public advertising of this drug. They ask for the co-operation of pharmacists in ensuring that the drug is made available to the public only under medical surveillance. The reason for the announcement is a recent American report recording the occurrence of "severe depressive reactions" in some patients treated for hypertension with *Rauwolfia serpentina* (*J. Amer. med. Ass.*, 1955, 159, 841).

**Fluoridation of Water at Watford.**—At a public meeting in Watford on November 20 a resolution was passed protesting at the proposal to introduce fluorine into the town's drinking-water.

**Blood Transfusion Centre at Brentwood.**—On November 17 Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, opened a new blood transfusion centre at Brentwood. It will eventually serve the whole of the north-east metropolitan area.

**Royal College of Surgeons.**—At the council meeting on November 10 Sir HARRY PLATT, P.R.C.S., reported that during his recent visit to the United States he had presented a diploma of honorary fellowship to Dr. FRED COLLER, professor of surgery at Michigan and a past president of the American College of Surgeons. An honorary fellowship was also awarded to Sir JOHN STOPFORD, vice-chancellor of Manchester University, whose diploma will be presented at the annual meeting of the College in Manchester on December 10 (see *Journal*, November 19, p. 1278).

**Institute of Child Health.**—The Simpson Smith Memorial Surgical Essay Prize for 1955, valued 100 guineas, has been awarded to Mr. H. H. NIXON, F.R.C.S., for his paper on "Intestinal Obstruction in the Neonatal Period." Mr. Nixon is paediatric surgeon to the Bromley Group of Hospitals.

**Leeds University.**—The following appointments were announced at the meeting of the university council on October 19: Mr. A. V. POLLOCK, lecturer in the department of surgery, and Dr. W. N. WILD, lecturer in anaesthetics.

**Sir Harry Platt, P.R.C.S.,** was awarded the honorary fellowship of the Royal College of Physicians and Surgeons of Canada at the annual meeting in Quebec on October 22.

**Professor F. W. Spiers,** professor of medical physics at Leeds, was elected president of the British Institute of Radiology at a meeting at the institute on October 20. He succeeds Dr. J. A. C. FLEMING, of St. Thomas's Hospital.

**Dr. R. R. A. Coombs,** of the department of pathology, Cambridge, was guest speaker at the annual meeting of the American Association of Blood Banks, held in Chicago from November 19 to 21. His subject was "The Antiglobulin Reaction."

**Dr. Macdonald Critchley,** neurologist to King's College Hospital, has gone to South America for a month's lecture tour sponsored by the British Council.

**Dr. A. Buchanan Barbour,** director of medical services for British European Airways, was appointed to the medical committee of the International Air Transport Association at its annual general meeting just held in New York. The appointment is for a period of two years.

**Dr. E. O'F. Walsh,** senior lecturer in the department of physiology at the Royal Free Hospital School of Medicine, has been appointed to the London University readership in biochemistry tenable at that School.

**By-election Candidate.**—Dr. J. D. MABON, 30, has been adopted as prospective Labour candidate for the by-election at Greenock caused by the death of Mr. Hector McNeil. Dr. Mabon, who graduated at Glasgow in 1954, stood unsuccessfully for Renfrewshire West at the general election in May.

**Change of Address.**—The address of the Association of Social Workers (formerly the British Federation of Social Workers) is now 25, Villiers Street, London, W.C.2.

## COMING EVENTS

**Society of Medical Officers of Health.**—Services Group annual dinner, 7 for 7.30 p.m., December 9, at R.A.M.C. Headquarters Mess, Millbank. Tickets (one guinea) from administrative officer of Society, Tavistock House South, Tavistock Square, London, W.C.1.

**Mental Health Conference.**—One-day conference on the role of local authorities in promoting mental health through health education, January 26, 1956, in the Old Library, B.M.A. House. Details from Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1.

**Institute of Dermatology.**—Semi-permanent exhibition on "Cytological Diagnosis in Dermatology," December 5–23.

**Radio.**—"Coronary Thrombosis and the Middle-aged Man," talk by Dr. J. N. MORRIS, director of M.R.C. Social Medicine Research Unit. Third Programme, December 1, at 8.35 p.m.

## NEW ISSUES

**British Journal of Industrial Medicine.**—The new issue (Vol. 12, No. 4) is now available. The contents include:

A CLINICAL STUDY OF A GROUP OF ACCIDENT-PRONE WORKERS. James A. Smiley.
COAL-MINERS' PNEUMOCONIOSIS IN FOUR COLLIERIES IN COUNTY DURHAM. R. I. McCallum and R. C. Browne.
THE ENERGY EXPENDED WHILE WALKING IN STOOPING POSTURES. Thomas Bedford and C. G. Warner.
TOLERANCE OF MEN TO WORK IN HOT, SATURATED ENVIRONMENTS WITH REFERENCE TO MINES RESCUE OPERATIONS. A. R. Lind, R. F. Hellon, J. S. Weiner, and R. M. Jones.
THE FORMATION OF PHOSGENE BY THE ACTION OF HOT SURFACES AND ITS ABSENCE WHEN TOBACCO IS SMOKED IN ATMOSPHERES CONTAINING CHLORINATED HYDROCARBON VAPOURS. J. Little.
OLDER PEOPLE AND HEAVY WORK. R. M. Belbin.
DERMATITIS FROM SOLUTIONS OF SODIUM AND CALCIUM CHLORIDE IN THE COAL-MINING INDUSTRY. O. P. Edmonds.
MISCELLANEA:
FOUR STUDIES OF THE RELATION BETWEEN PSYCHOLOGICAL AND OCCUPATIONAL HANDICAP AMONG INDUSTRIAL WORKERS. Alastair Heron.
A METHOD FOR THE DETERMINATION OF CARBON MONOXIDE IN BLOOD. P. J. Lawther and G. H. Apthorp.
BRITISH OCCUPATIONAL HYGIENE SOCIETY: THE ASSESSMENT OF HEALTH AND DISEASE IN INDUSTRY.
THE DISEASES OF OCCUPATIONS. A Review by Richard Schilling.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

## SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

### Monday, November 28

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF ANAESTHETICS.—8 p.m., Dr. J. A. Lee: Anaesthetic Out-patient Clinics.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—4.30 p.m., Mr. J. H. M. Beattie: Functional Uterine Haemorrhage.
INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. E. Stengel: postgraduate lecture-demonstration.
LONDON UNIVERSITY.—At Senate House, 6 p.m., special university lecture by Professor J. Nuttin (Louvain): Motivation and Cognitive Factors in Human Behaviour.
MANCHESTER MEDICAL SOCIETY.—At Manchester University, (1) 5 p.m., Section of Odontology. Dr. M. J. F. McArdle: Facial Neuralgia. (2) 9 p.m., Section of General Practice. Dr. C. E. B. Rickards: Out-patient Gynaecology.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, 5.30 p.m., Dr W. S. Feldberg, F.R.S.: Role of Mediators in the Inflammatory Tissue Response.

### Tuesday, November 29

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. G. S. Dawes: Physiological Effects of Anoxia in the Foetal and Newborn Lamb.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. F. R. Bettley: Eczema-Asthma Syndrome.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Professor C. A. Keele: Therapeutics of Pain.
LONDON UNIVERSITY.—At Senate House, 6 p.m., special university lecture by Professor J. Nuttin (Louvain): Motivation and Cognitive Factors in Human Behaviour.
●OXFORD UNIVERSITY MEDICAL SOCIETY.—At Radcliffe Infirmary, 8.15 p.m., Symposium: Thinking. Speakers, Professor Gilbert Ryle, Dr. R. G. McInnes, Sir Wilfrid Le Gros Clark, F.R.S., and Mr. B. A. Farrell.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arris and Gale Lecture by Dr. F. Dudley Hart: Hormone Replacement Therapy in the Surgery of Endocrine Disorder.
ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Westminster Medical School, 5.30 p.m., Dr. A. H. T. Robb-Smith: From Graunt to Geneva (A History of Disease Classification).
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. A. M. Claye: Disturbances of Sexual Function.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. B. G. Parsons-Smith: Neurological demonstration.

### Wednesday, November 30

EDINBURGH CLINICAL CLUB.—At Jordanburn Hospital, 4 p.m., clinical meeting conducted by Professor Alexander Kennedy.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. J. R. Belcher: Cyanotic Congenital Heart Disease.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann: Ulcerative Granulomatous Conditions of the Nose.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. G. Hanley: Urological Problems in Pregnancy.
LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal College of Surgeons of England, 8.15 p.m., Presidential Address by Miss Gwendoline Smith: From Barbers to Surgeons.
LONDON UNIVERSITY.—At Senate House, 6 p.m., special university lecture by Professor J. Nuttin (Louvain): Motivation and Cognitive Factors in Human Behaviour.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.30 p.m., Brains Trust. Team, Dr. E. Bulmer, Mr. A. L. d'Abreu, Dr. M. J. Meynell, and Dr. M. Sim.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. P. M. F. Bishop: Endocrinological Investigations.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Dr. P. R. Peacock: Possible Actiological Factors in Lung Cancer.

### Thursday, December 1

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. Walker: Oxygen Environment of the Foetus.
FACULTY OF HOMOEOPATHY.—At Royal London Homoeopathic Hospital, 5 p.m., Dr. Andrew Brown: Trend of Disease since Hahnemann.
GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—7.30 p.m., Professor I. Donald: Clinical Alarm.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., symposium: Anxiety States. Openers, Dr. C. H. Stewart-Hess and Dr. F. Hopkins.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.30 p.m., Otolaryngology Lecture by Dr. S. P. Meadows: Cranial Palsies and Otolaryngology.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Queen's College, Dundee, 5 p.m., Professor G. P. Boddie: Eradication of Bovine Tuberculosis.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. H. Paterson: postgraduate demonstration in neurology.
ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY.—4.30 p.m., demonstration and discussion of clinical cases.

### Friday, December 2

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. S. C. Gold.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Sir Clement Price Thomas.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical meeting for general practitioners. Dr. C. H. Edwards: Headaches and Neuralgias.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—3 p.m., Mr. S. A. Way: Intraepithelial Carcinoma.
LONDON UNIVERSITY.—At Charing Cross Hospital Medical School, 5 p.m., special university lecture in human anatomy and morphology by Dr. R. K. Burns (Washington): Experimental Studies of Sex Differentiation in the Opossum.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 2 p.m., Mr. H. J. B. Atkins: Research into Breast Cancer. (2) 4 p.m., Dr. A. G. MacGregor: Radioactive Iodine Therapy.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: WELSH BRANCH.—At 195, Newport Road, Cardiff, 6.30 p.m., Dr. R. C. Wofinden: The William Budd Health Centre.
SOUTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—At 13, Portland Place, W., 8 p.m., Dr. John Burton: Health Education in the U.S.S.R.; Dr. S. Gottlieb: General Practice in the U.S.S.R.
WELSH NATIONAL SCHOOL OF MEDICINE.—At Institute of Pathology, Royal Infirmary, Cardiff, 5 p.m., Kettle Memorial Lecture by Professor J. H. Dible: Ischaemia in the Peripheral Circulation.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. A. E. Mourant: Relation Between Blood Groups and Disease—A New Factor in Medicine.

## APPOINTMENTS

BROWN, JOHN RUSSELL, M.B., Ch.B., Assistant Divisional Medical Officer, Lancashire County Council.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—J. W. Beattie, M.D., M.R.C.P., Consultant Physician in Geriatrics, Norfolk and Norwich Area; J. P. Stephens, M.Chir., F.R.C.S., Consultant Surgeon, Norfolk and Norwich Hospital Group; I. P. Williams, M.B., B.Chir., M.R.C.P., D.M.R.D., Consultant Radiologist, Newmarket General Hospital and Saffron Walden General Hospital; P. H. Blakiston, F.F.A.R.C.S., M.R.C.S., L.R.C.P., D.A., Consultant Anaesthetist, Newmarket and Bury St. Edmunds Area; P. E. Rixon, M.B., Ch.B., Registrar in Psychiatry, Hellesdon Hospital; K. R. S. Pool, M.B., B.S., Surgical Registrar, Norfolk and Norwich Hospital; P. B. Counsell, M.S., F.R.C.S., Consultant Surgeon, Ipswich and East Suffolk Hospital Group; Anne K. Kirkland, M.B., Ch.B., D.P.M., Senior Registrar in Mental Deficiency and Child Psychiatry, Little Plumstead Group of Hospitals; L. F. W. Rowe, M.B., Ch.B., Senior Registrar in Psychiatry, St. Andrew's Hospital; J. F. Dunn, M.B., Ch.B., Senior Registrar in Psychiatry, Hellesdon Hospital; C. Galvin, M.Ch., F.R.C.S., Senior Surgical Registrar, United Norwich Hospitals; J. A. M. Martin, M.B., B.S., D.L.O., Registrar in Ear, Nose, and Throat Surgery, Norfolk and Norwich Hospital and Jenny Lind Hospital; S. A. R. Gardezi, M.B., B.S., Surgical Registrar, Peterborough Memorial Hospital; M. R. H. Mahmood, M.B., B.S., Radiological Registrar, Ipswich and East Suffolk Hospital (Anglesea Road Wing).

GALLAGHER, J. E., M.B., B.Ch., B.A.O., D.P.H., D.C.H., Assistant County Medical Officer, Dublin County Council.

HARGREAVES, EDWARD ARTHUR, M.R.C.S., L.R.C.P., D.P.H., Medical Officer of Health, Lexden and Winstree Rural District and Wivenhoe and West Mersea Urban Districts, and Assistant Medical Officer of Health, Essex County Council.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Pezeshgi.**—On November 10, 1955, at Avenue Churchill, Teheran, to Elizabeth, wife of Dr. H. Pezeshgi, a sister for Jila—Sheerin.
**Warner.**—On November 14, 1955, at Bristol Maternity Hospital, to Amy, wife of Dr. James Warner, a daughter—Jennifer Ann.

### DEATHS

**Bryan.**—On October 25, 1955, Clement Arthur Douglas Bryan, M.R.C.S., L.R.C.P., of 17, The Chilterns, Brighton Road, Sutton, Surrey.
**Clark.**—On October 25, 1955, James Thomson Doran Clark, M.B., Ch.B., D.P.M., of 24B, Holland Park Road, London, W.
**Cruickshank.**—On October 22, 1955, accidentally drowned at Singapore, James Durno Cruickshank, M.D., D.T.M.&H., Lieutenant-Colonel, R.A.M.C., aged 44.
**Goldie.**—On October 18, 1955, in hospital, William Nicholas Murray, M.B., Ch.B., of 3, High Bank, Denton, near Manchester, Lancs, aged 54.
**Greenop.**—On October 26, 1955, at King's College Hospital, London, S.E., Roland Morley Greenop, M.R.C.S., L.R.C.P.
**Mackenzie.**—On October 25, 1955, William Mackenzie, M.D., F.R.C.S.Ed., D.P.H., of 34, High Street, Gosforth, Newcastle-upon-Tyne, Northumberland.
**Miller.**—On October 27, 1955, at 5, Ardross Terrace, Inverness, Robert Webster Miller, M.B., Ch.B.
**Morgan.**—On October 29, 1955, Edgar John Morgan, M.B., Major, I.M.S., retired, of 15, Grange Court, Cambridge, aged 85.
**Rea.**—On October 28, 1955, at the Norfolk and Norwich Hospital, Reginald Hans Taylor Rea, M.B., M.R.C.P.
**Ridley.**—On October 18, 1955, in London, John Ridley, M.B., B.S., of Russet Lodge, Lindisfarne Road, Jesmond, Newcastle-upon-Tyne.
**Thompson.**—On October 28, 1955, at his home, St. Paul's Square, Burton-on-Trent, Frederick Charles Victor Thompson, L.M.S.S.A.

# Any Questions?

*We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.*

### Anxiety about Small Genitals

**Q.**—*Can treatment have any effect on underdeveloped male external genitalia, a condition usually associated in my experience with unsatisfactory sexual relationships and neurosis?*

**A.**—The first thing to make sure of is that the patient's observations are objective and that the genitalia are really appreciably below the average, remembering that the normal limits are wide. In the experience of the writer, most patients with this complaint are really suffering from psychological impotence and have normal genitals in fact.

Where the genitals are really small, one has to consider whether this is part of a major endocrine disorder such as partial eunuchoidism or relative infantilism. In these conditions, in which there is a defective secretion of androgens, there should be other evidence of this, such as poor development of sexual hair and of musculature, and the 17-ketosteroids in the urine should be on the low side. In such cases the response to testosterone or methyl-testosterone is dramatic. Libido, potency, and the size of the penis all increase, but the testes are unaffected or may even become smaller. In other cases, where there is no deficiency of androgens, there will be no result whatsoever from this therapy. This is also true of those cases where the genital organs are relatively refractory to a normal androgen stimulus.

### Exploration and Drainage of the Common Bile Duct

**Q.**—*Should the common bile duct invariably be drained after cholecystectomy?*

**A.**—The common bile duct should, most emphatically, not be drained routinely after cholecystectomy. The great majority of surgeons do, however, drain the abdomen after cholecystectomy, though even this step is not invariable. The crux of this question lies in the indications for exploring the common bile duct, since drainage of the duct should only be done after this.

In general it may be said that the common duct should be explored whenever operation reveals positive evidence or suspicion of disease in it. After exploration it is usual to establish T-tube drainage because natural drainage into the duodenum is likely to be impaired for a while owing to oedema of the duct following manipulation and, if present, pre-existing infection. The tube is generally removed between the tenth and fourteenth days after operation, provided drainage by the normal route has been established.

The specific indications for common duct exploration at the time of cholecystectomy may be: (1) The presence of jaundice. (2) A dilated or thickened common duct. (3) When aspiration of the duct yields turbid bile. (4) When clinical findings suggest cholelithiasis but no stones are found in the gall-bladder (it should be emphasized that stones are often difficult to feel through the wall of the organ). (5) When the gall-bladder contains biliary mud or stones of smaller calibre than the cystic duct. With regard to jaundice, many patients with gall-bladder disease who have had jaundice show no evidence of disease in the common duct, but almost half of those with stones in the common duct have a history of jaundice.

However skilled and careful the surgeon, a proportion of explorations of the common duct will disclose no abnormality, but those with extensive experience of this procedure are satisfied that the theoretical risks of a negative exploration—and in skilled hands the risks are almost entirely theoretical—are far outweighed by the number of cases in which stones or some other abnormality is discovered. Nevertheless, in an attempt to reduce the number of negative explorations, some surgeons advocate routine cholangiography on the operation table before the gall-bladder is removed; but even this is not infallible. If sole reliance is placed upon cholangiography, stones may be overlooked since they can be hidden by the opaque medium, and even a free flow of bile into the duodenum does not rule out the possibility of a stone in the duct. Cholangiography on the operation table can sometimes be a valuable adjunct, but at the present time most surgeons use it only selectively, if at all.

Provided the ducts have been properly handled and a T-tube of suitable type and calibre has been used, complications directly due to drainage are negligible. The patient whose common duct is drained may spend a little longer in hospital than the straightforward case; but, if stones have been removed from the duct, this is no objection to drainage. If exploration proves negative, some surgeons do not drain the duct provided it is quite normal and the bile clear. This is a matter for individual judgment; in any case the tube can usually be removed after seven days, and need rarely delay the patient's discharge.

### Significance of Positive Gonococcal Complement-fixation Test in Absence of Signs of Clinical Disease

**Q.**—*What treatment is advised for a patient with a strongly positive gonococcal complement-fixation test, but without other signs of gonorrhoea?*

**A.**—Provided thorough laboratory investigations (which must include cultures of the secretion) have been carried out by an expert and found to be negative, a strongly positive gonococcal complement-fixation reaction should be ignored. It is not stated whether the patient is male or female: if a woman the attempt to culture organisms should be repeated.

In all probability the patient was a sufferer from gonorrhoea in the pre-chemotherapy era, and during the long irrigation treatment a large amount of antibody was formed. Gonococcal antibodies in such cases may persist for months, years, or even throughout life: it is not necessary for an infective focus to coexist.

### Amniotic Fluid Embolism and Post-partum Haemorrhage

**Q.**—*According to recent reports amniotic fluid may enter the maternal blood stream, causing defibrination of blood and subsequent post-partum haemorrhage. In a recent case a primipara had a precipitate labour, an anaesthetic being administered within two hours of its commencement. The child was extracted by forceps but was dead, and a severe post-partum haemorrhage followed. In a discussion I disagreed with the view that the haemorrhage was due to amniotic embolus and bore no relation to the anaesthetic and the non-contracting uterus—a view justified on the laboratory report of defibrinated blood. What is the current opinion on administering an anaesthetic early in the first stage of precipitate labour? Would the consequent relaxed uterus favour amniotic infusion through open vascular spaces after delivery by forceps?*

**A.**—In the reported cases of amniotic fluid embolism an outstanding feature has been that the labour pains were very strong. It is this which is held to force the liquor into the maternal blood spaces, the embolism being evidenced by symptoms such as dyspnoea and mild cyanosis as well as signs of shock. The occurrence of amniotic infusion into the relaxed uterus after delivery by forceps, as suggested, is therefore unlikely. It would be helpful to know the total duration of labour in this case, but if it was under three hours, a time suggested as the upper limit for precipitate labour, then the anaesthetic was rightly given at the right time. The most appropriate time to induce anaesthesia is shortly before full dilatation, and it should not be on too deep a plane.

The hypofibrinogenaemia in this case may have been due either to amniotic embolism or perhaps accidental haemor-

rhage; and the subsequent bleeding may have been due to this or to uterine atony, or both. The risk of atonic post-partum haemorrhage following delivery under general anaesthesia can be minimized by the prophylactic intravenous injection of 0.5 mg. ergometrine as soon as the head is crowned or the anterior shoulder delivered.

### Treatment of Ichthyosis

**Q.**—*What is the best treatment for ichthyosis?*

**A.**—Simple ichthyosis, the severe form of xeroderma, is often susceptible to climatic variation and may improve spontaneously in a warm and humid climate. There is much individual variation, and the ability to sweat bears upon the problem. Some patients improve on vitamin A therapy.

The most effective local treatment is the application, after a warm bath, of a mixture of mineral, vegetable, and animal fats such as the following, covered by a clinging stockinette stocking and vest type of dressing: 10 gr. (0.65 g.) of salicylic acid to the ounce (31 g.) of a mixture of equal parts of lanolin, olive oil, glycerin, ung. emulsificans (*B.P.*), and soft paraffin.

Milder degrees of the affection will be relieved by applications containing glycerin.

### Mercury from a Broken Thermometer

**Q.**—*I understand that, while mercurial salts are poisonous, mercury itself is harmless when ingested by mouth. If a clinical thermometer is broken in a child's mouth is there no need to worry about any swallowed mercury?*

**A.**—Mercuric salts—for example, mercuric chloride (corrosive sublimate)—are soluble and toxic. Mercurous salts—for example, mercurous chloride (calomel)—are insoluble and less toxic. Metallic mercury is used in such preparations as hydrarg. cum cret., and it is not itself poisonous. It may, however, be converted into a poisonous salt if it remains in the body for a long time.

There is therefore no need to worry about any swallowed mercury when a thermometer breaks in a child's mouth. Elimination of the mercury may be hastened by a simple saline purgative.

### Weight Gain in Babies

**Q.**—*Babies are now said to be doubling their birth weight much earlier, and paediatricians are recommending a daily milk intake of 3 oz. instead of 2½ oz. per lb. (185 ml. instead of 153 ml. per kg.) body weight. (a) Are breast-fed babies gaining weight as fast as the bottle-fed babies? (b) Is this rapid weight gain desirable?*

**A.**—This question seems to reveal some misapprehension of the principles of infant feeding as they are being taught at the present day, and there is reason to think that this misapprehension is fairly common. Successfully breast-fed babies gain weight just as fast as bottle-fed babies, and many of them, breast- or bottle-fed, double their birth weight in four months. There is no reason to think that this is not a perfectly natural phenomenon which occurred in the past just as it does now. Furthermore, in the first two or three months of life many babies, in the past as well as now, required at least 3 oz. of milk per lb. (185 ml. per kg.) in order to remain contented and happy and gain weight satisfactorily.

In the recent past, however, before the frequency of infection as a cause of infantile disorders, and the many other organic and biochemical causes of vomiting and failure to thrive, were as well known as they are to-day, overfeeding was thought to be a potent cause of ill-health. The average intake of milk on which most babies thrive in the first six months became accepted as the right amount that they ought to have during the whole period. Doctors tended to forget that during the first two months or so of very rapid growth many babies required more than the average intake. They also tended to forget that 2½ oz. per lb. (153 ml. per kg.) was the average intake for the average baby, and that as babies are by no means standardized some required much more, and some rather less, in order to thrive.

We do not know the optimum weight gain for any baby, but it probably varies within fairly wide limits. It is likely that, if a baby is gaining 4 to 8 ounces (113 to 227 g.) a week, is contented, is not constipated, and looks well, it is being properly fed. The guide to success in feeding babies is now, as it always has been, the condition of the individual baby itself. The knowledge of average calorie and fluid intakes and weekly weight gains is extremely useful to help decide what is wrong if a baby is not doing well.

### Viscous Semen

**Q.**—*What is the treatment in a sterile marriage of a man who produces a semen normal in all respects except that it fails to liquefy, even after 24 hours? The count cannot be performed until after the addition of hyaluronidase, which makes the specimen slightly less mucoid but does not liquefy it, although dispersion of sperms is rendered possible. I understand that this is due to a defect in mucolytic enzymes produced by the accessory glands of the seminiferous tract. There is neither history nor evidence of disease of prostate gland, seminal vesicles, or Cowper's glands.*

**A.**—It is to be presumed that the semen in question remains highly mucoid in consistence, rather than that it remains in the semi-solid state (seen by phase-contrast microscopy to consist of masses of fibres[1]) typical of freshly ejaculated semen. Little or nothing is known why some samples of semen remain highly viscous in this way, but it appears to have nothing to do with lack of the normal fibrinolytic enzyme. Further, it may have no bearing on infertility, since a normal post-coital test may be obtained even when the semen remains highly viscous. No treatment is known which will alter this seminal characteristic.

REFERENCE

[1] Oettlé, A. G., *Fertil. and Steril.*, 1954, **5**, 229.

### Toothbrushes and Toothpaste

**Q.**—*What instructions should be given to children about brushing their teeth? Is there any formula for a rather less expensive toothpaste than the proprietary brands?*

**A.**—The toothbrush has two main functions: (1) to help clear away debris from round the teeth, and (2) to massage the gums. Of these probably the latter is of greater importance. In the ordinary way, the movements of tongue and cheeks, in addition to the salivary flow, are the main factors in getting rid of food debris. The toothbrush can assist this process, though the areas which it is most desirable to reach—that is, interstitial spaces between the teeth, deep fissures on the biting surface, etc.—cannot in fact be reached by the brush. From the point of view of prophylaxis against dental caries, the toothbrush can be a valuable adjunct, but should not be regarded as the mainstay of defence, and finishing a meal with fibrous foods, rather than soft, sticky material, is of greater value. Unfortunately, civilized diet does not appear to have an adequate frictional effect on the gums and a toothbrush is valuable in this respect as providing massage, helping to maintain a good blood supply, and keeping them healthy. The more the gums are brushed the better, and, while it is often advocated that the teeth should be brushed after every meal, this is often impracticable. The most important time is last thing at night, before going to bed. The direction of brushing should be from the gums towards the biting edges of the teeth—that is, downwards in the upper jaw and upwards in the lower.

There have been suggestions that bristle brushes are better than nylon ones, owing to a possible cutting action of the nylon bristles, but clinical proof of this suggestion cannot easily be obtained.

As an inexpensive agent for brushing the teeth, common salt can be used, or even a little soap if the taste does not prove too unpleasant. If a rather more elegant preparation

is required for a dentifrice, the following simple prescription can be used: sodium bicarbonate, 60 gr. (4 g.); thymol, 10 gr. (0.65 g.); hard soap, 60 gr. (4 g.); saccharin, 4 gr. (0.26 g.); with precipitated chalk to make it up to 2 oz. (62 g.).

### Simultaneous Diphtheria-Pertussis Immunization and Vaccination against Smallpox

**Q.**—*I usually give the first injection of diphtheria pertussis prophylactic at the time of vaccination against smallpox, the age of the child being 4–5 months. I have never noticed any unpleasant effects from this. Are there any contraindications to immunization and vaccination as outlined above?*

**A.**—Although unpleasant effects have not been observed hitherto by the questioner, his method probably incurs a certain risk.

As a general rule smallpox vaccination should be done first, say, at about the third or fourth month, and this may be followed after at least three weeks by the first injection of a course of diphtheria–pertussis or, preferably, diphtheria–tetanus–pertussis prophylactic. The number of infant vaccinations in England and Wales is still deplorably low, and it would therefore be unfortunate if immunization schemes were to receive any set-back from "accidents" that might be aggravated by, or could be ascribed to, the administration of another prophylactic at the same time as smallpox vaccine.

### Femoral Thrombosis and Flying

**Q.**—*Does a history of femoral thrombosis in the past preclude a patient from flying? A patient who had a femoral thrombosis post-operatively nearly two years ago is now quite well, apart from occasional attacks of oedema of the affected leg. She is anxious to fly from Singapore to England, but has been told she must never travel by air again.*

**A.**—A post-operative femoral thrombosis which occurred as long ago as two years and has now resolved except for occasional attacks of oedema of the affected leg is no bar to travel by air for long distances, provided precautions are taken. Even in normal individuals sitting in aircraft seats swelling of the feet occurs during a long flight, owing to the dependent position of the legs and the continued pressure of the seat on the under surfaces of the thighs interfering with the return of the blood and lymph. The degree of oedema of the feet is greater in those with defects of circulation, anaemia, and anoxaemia. This lady can travel safely by air if she takes the precaution to keep her legs raised, preferably to the level of the seat. This can be attained by a simple support like the detachable extension of a deck chair or a small folding camp stool, or by piling up small luggage and cushions, then covering these with a rug. The best method, however, is to have either a sleeping-berth or an invalid couch: the latter consists of occupying two facing seats and bridging the gap with a special insertion as provided by certain airlines. There is, of course, an extra charge for a sleeping berth or the invalid couch. In addition, travel in a pressurized aircraft is advisable to avoid anoxia, which aggravates any tendency to oedema in direct proportion to the altitude of flight. In pressurized aircraft the simulated altitude is not likely to exceed that of 8,000 ft. (2,400 metres) at any time. It is advisable to get into touch beforehand with the airline concerned to solicit their aid in making suitable seating arrangements for the patient.

### Onychogryphosis

**Q.**—*What is the treatment and prognosis of onychogryphosis affecting all the nails of the feet in a child aged 3?*

**A.**—This is a most unusual complaint. It is assumed, since no mention is made of lesions on the finger-nails or elsewhere on the skin, that these are normal. It seems likely that onychogryphosis affecting all the toe-nails in a child is inborn and may be familial. Careful recording of such cases may be of considerable importance in genetics, and this aspect of the case should be carefully inquired into. Records of such cases are rare. If this case is of that nature, then recovery is never likely to occur, with or without treatment. Treatment is symptomatic and consists in trimming the nails with scissors, knife, file, or sandpaper, whichever may be found most convenient. *X*-ray treatment may have some effect. It would be justifiable to treat one or two nails, giving a total dose of 600 to 800 r in divided doses to the region of the nail bed and matrix. If the effect is satisfactory, treatment may then be given to the other nails.

Other types of nail thickening may be produced by a great variety of skin disorders, such as psoriasis, eczema, or tinea, though the lesions thus produced do not closely resemble onychogryphosis. In such cases the treatment and prognosis depend on the nature of the underlying condition.

### Difficulty in Swallowing after Carcinoma of Larynx

**Q.**—*What treatment is advised for a man with apparently healed carcinoma of larynx who has great difficulty in swallowing liquids; attempts to do so cause troublesome cough. He takes solids well.*

**A.**—It is assumed that this patient has been treated by radiotherapy. The site of the neoplasm is not stated, but if it was an extrinsic growth then the probability is that fibrosis of the glottis has occurred following the irradiation. Alternatively the inability to close the glottis fully during the swallowing of liquids may be due to recurrence of growth. Direct laryngoscopy would seem to be advisable.

If fibrosis is the cause there is really nothing which can be done, though sipping the liquids in small amounts may prevent them "going the wrong way." Should all swallowing become impossible, or if recurrence has occurred, then laryngectomy will be necessary.

### Colostomy Patients and Swimming Baths

**Q.**—*Should a man with a colostomy be allowed to bathe in a public swimming-bath?*

**A.**—By the time that a patient with a colostomy begins to think about resuming swimming it can be taken for granted that he has become confident in his colostomy routine and management. If his general health is good a resumption of all normal out-of-door activities is to be encouraged, and there is no objection to such a patient swimming either in the sea or in a public swimming-bath. For the occasion, the colostomy may be covered with a small square of gauze, and this is then sealed over with a couple of strips of 2 in. or 3 in. (5 or 7.5 cm.) "elastoplast" or one of the waterproof adhesives such as "sleek." A patient with a colostomy is not likely to want to enter a swimming-bath if he is in a phase of intestinal upset or irregularity, and for his own good he might be warned not to stay in the water overlong or risk a chill subsequently by dawdling on the side. Particular care in diet should be advised before and after swimming, with no experiments in regard to fruit, vegetables, or drinks, in order to ensure that the motions are formed or slightly constipated.

## NOTES AND COMMENTS

**Metabolism of Hair.**—In the reply to a question on this subject ("Any Questions?" October 29, p. 1099) tyrosine was wrongly included among the sulphur-containing amino-acids; it contains no sulphur.

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